Basic Principles of Human Health Risk Assessment for Environmental Chemical Mixtures, and Aggregate and Cumulative Risk Assessments

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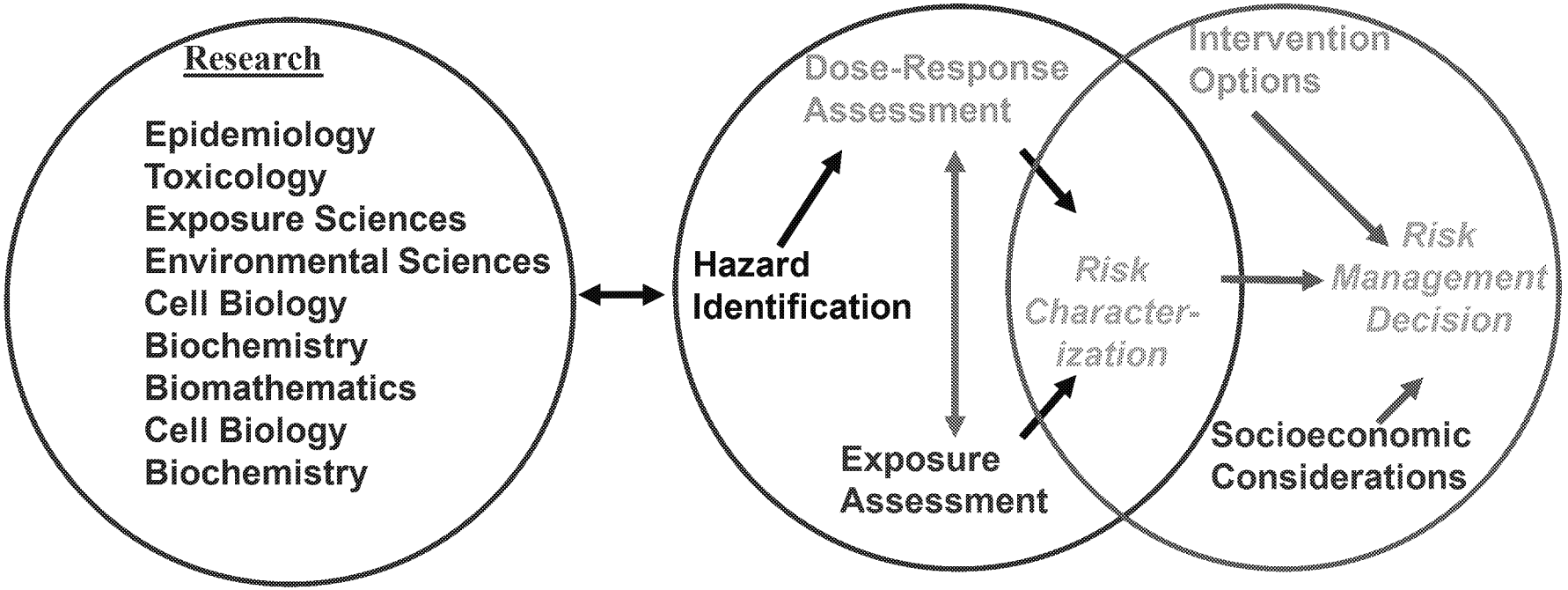
Agenda

1. Introduction
2. Overview of Chemical Mixtures Risk Assessment
   A. Component Methods
   B. Fraction Methods
   C. Whole Mixture Methods
   D. Sufficient Similarity Methods
3. Cumulative Risk Assessment
4. Supplemental Materials
   A. Pathogens and Physical Agents
   B. Cumulative Risk Assessment Case Study

Human Health Risk Assessment: Research and Decision Contexts



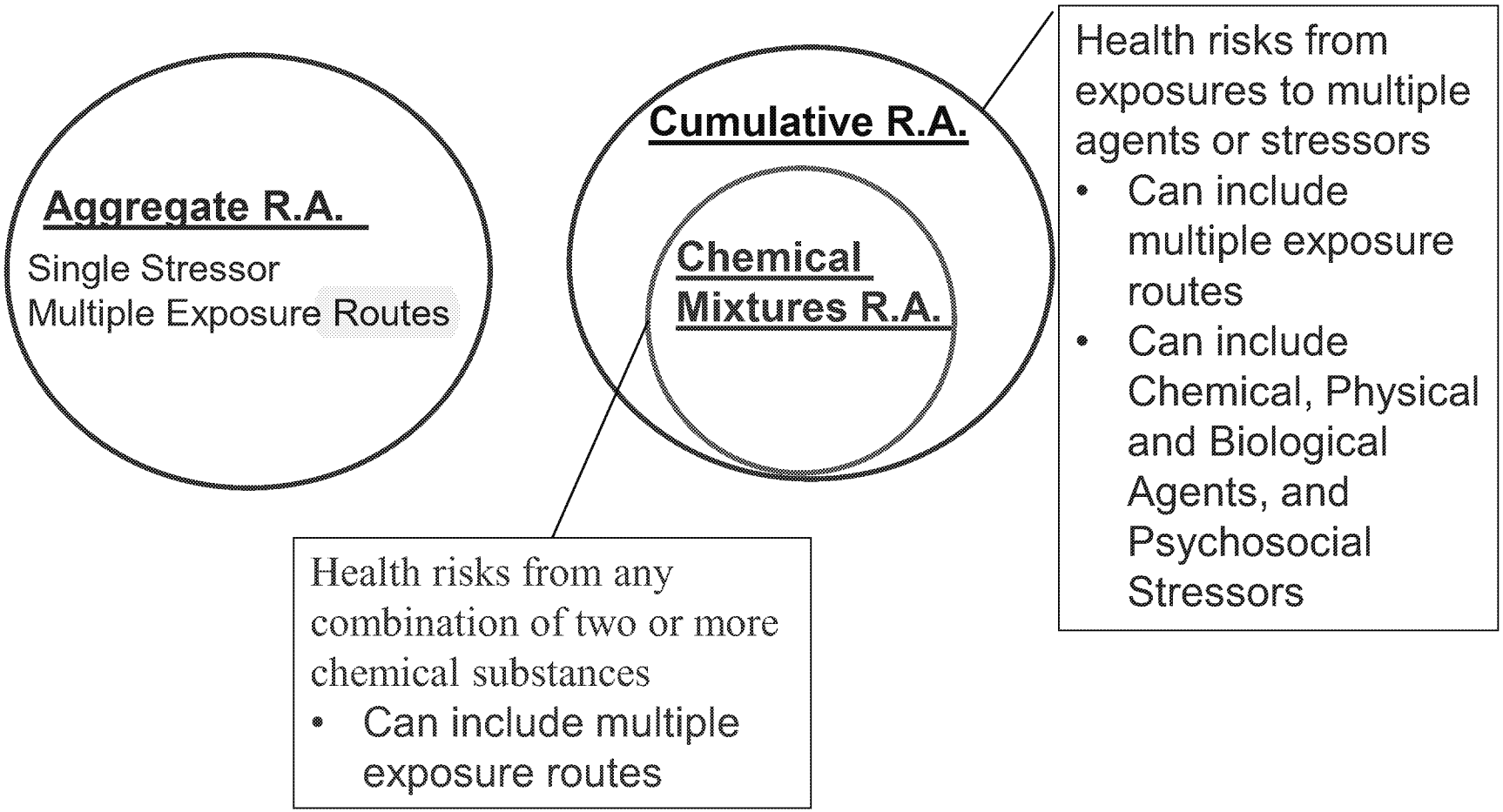
Explanation of Terms

- **Chemical mixtures** - "any combination of two or more chemical substances regardless of source or of spatial or temporal proximity"
  - Range from combinations of a few compounds to highly complex mixtures consisting of hundreds of compounds, some of which may not be identified chemically
    - US EPA (1986) Chemical Mixtures Risk Assessment Guidelines

- **Aggregate exposure** – "Combined exposure of an individual or population to a specific agent or stressor via relevant routes, pathways, and sources"; **aggregate risk assessment** an analysis of risk posed by aggregate exposure to a single agent or stressor"

- **Cumulative risk** – "Combined risks from aggregate exposures to multiple agents or stressors"; **cumulative risk assessment** "an analysis, characterization, and possible quantification of combined risks to health or environment from multiple agents or stressors"
  - US EPA (2003) Framework for Cumulative Risk Assessment

Cumulative, Aggregate, and Chemical Mixtures Risk Assessments



Human Health Risk Assessment of Environmental Chemical Mixtures

ORIGINS OF CHEMICAL MIXTURES

Intentional

- Manufactured products
  - PCBs
  - brominated flame retardants
- Pesticide formulations
  - technical grade toxaphene
- Fuels
  - gasoline
  - jet fuel

Incidental (Generated)

- Byproducts
  - drinking water disinfection byproducts
  - volatile organic compounds
- Combustion
  - dioxins
  - PAHs
  - diesel exhaust
- Product degradation
  - weathered toxaphene

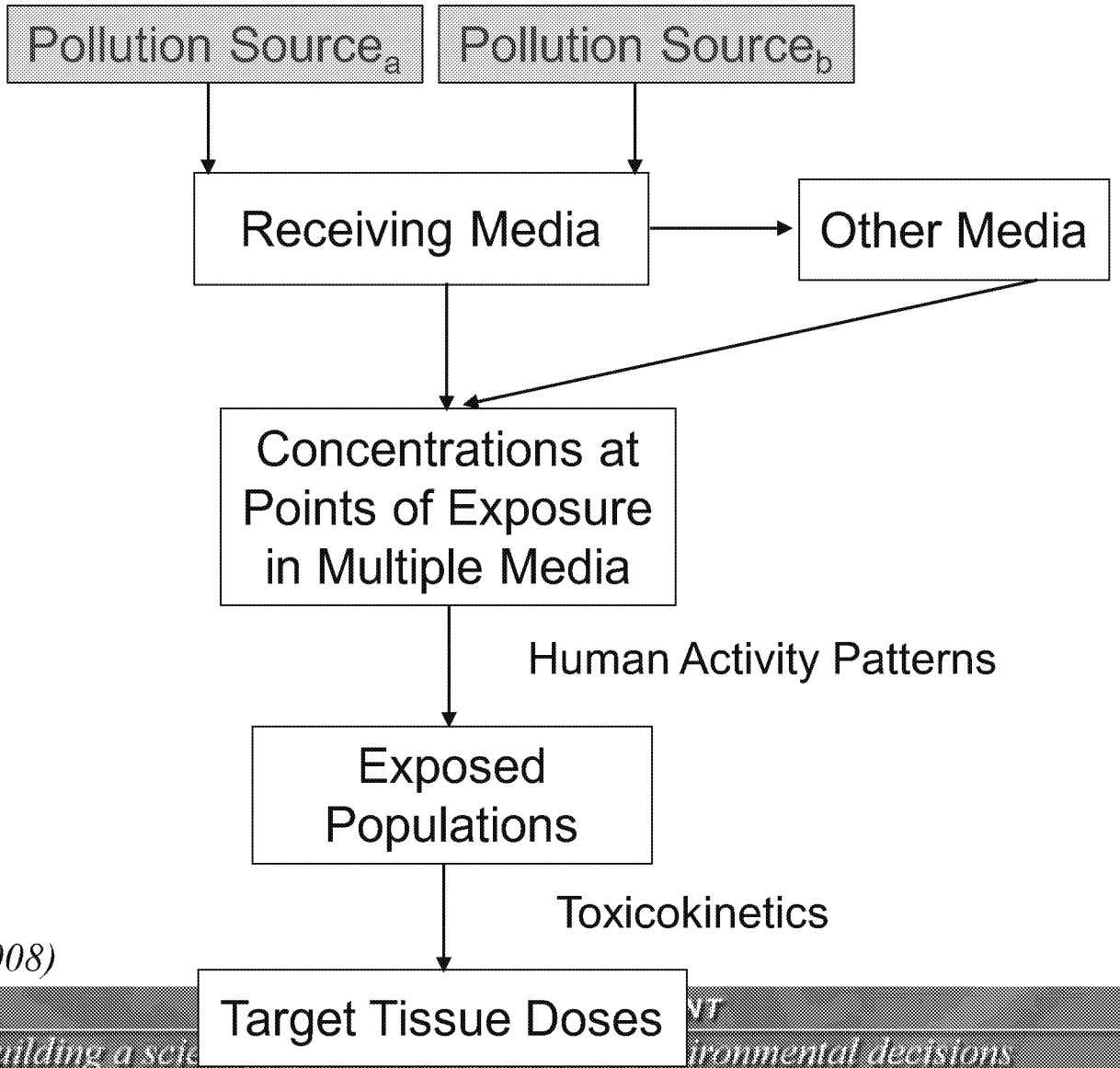
Coincidental

- Urban air
- Superfund sites
  - VOCs
  - radionuclides, metal mixtures
- Mine tailings
  - metal mixtures

ATSDR (2004)

Pollutants that coexist in the same medium, from different sources

MIXTURE EXPOSURE ASSESSMENT
Conceptual Model



Source: *Rice et al. (2008)*

MIXTURES FATE AND TRANSPORT

- Environmental mixtures can change over time

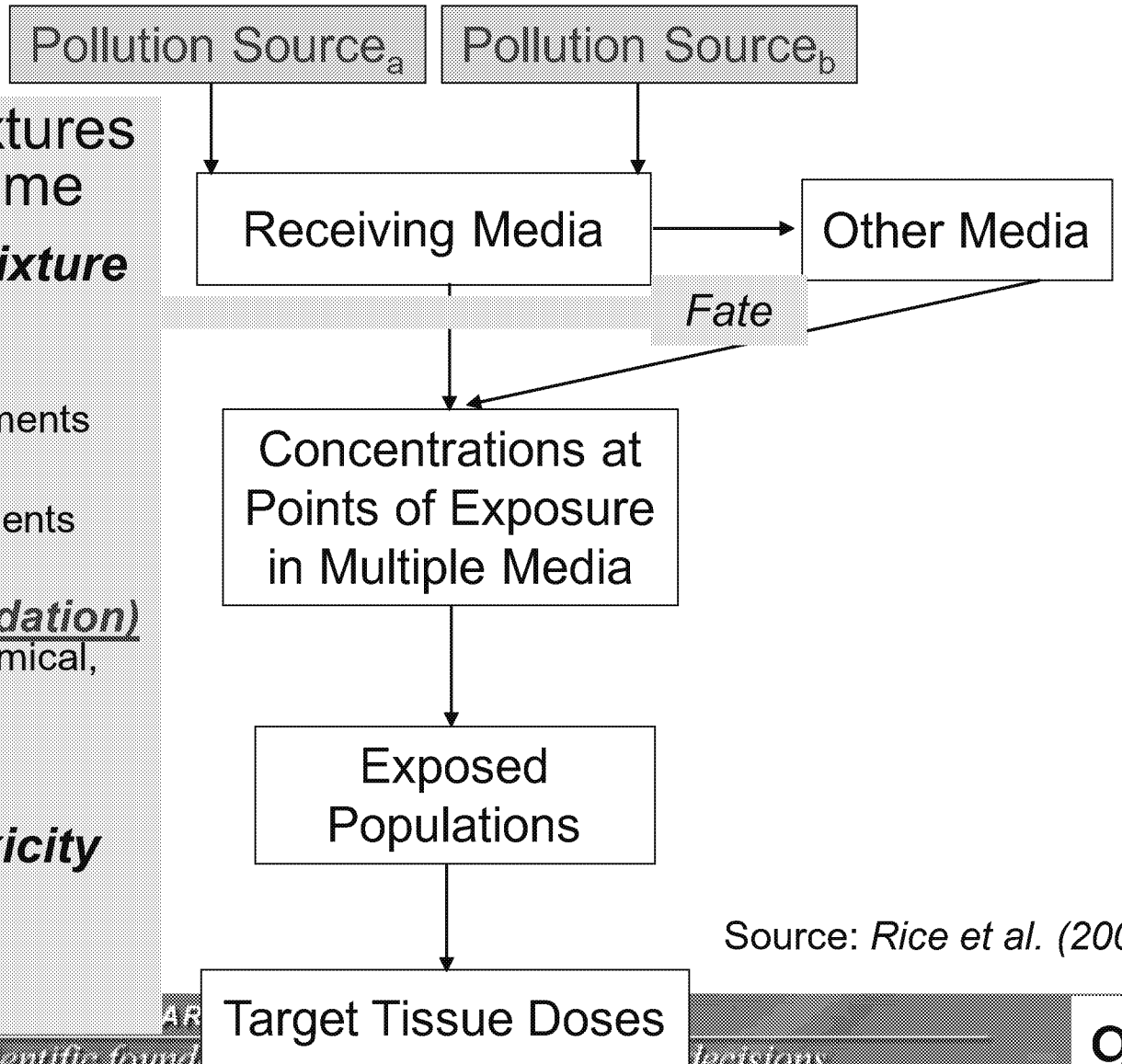
Differential fate of mixture components

Transport
through individual compartments

Partitioning
transfer between compartments (abiotic and biotic)

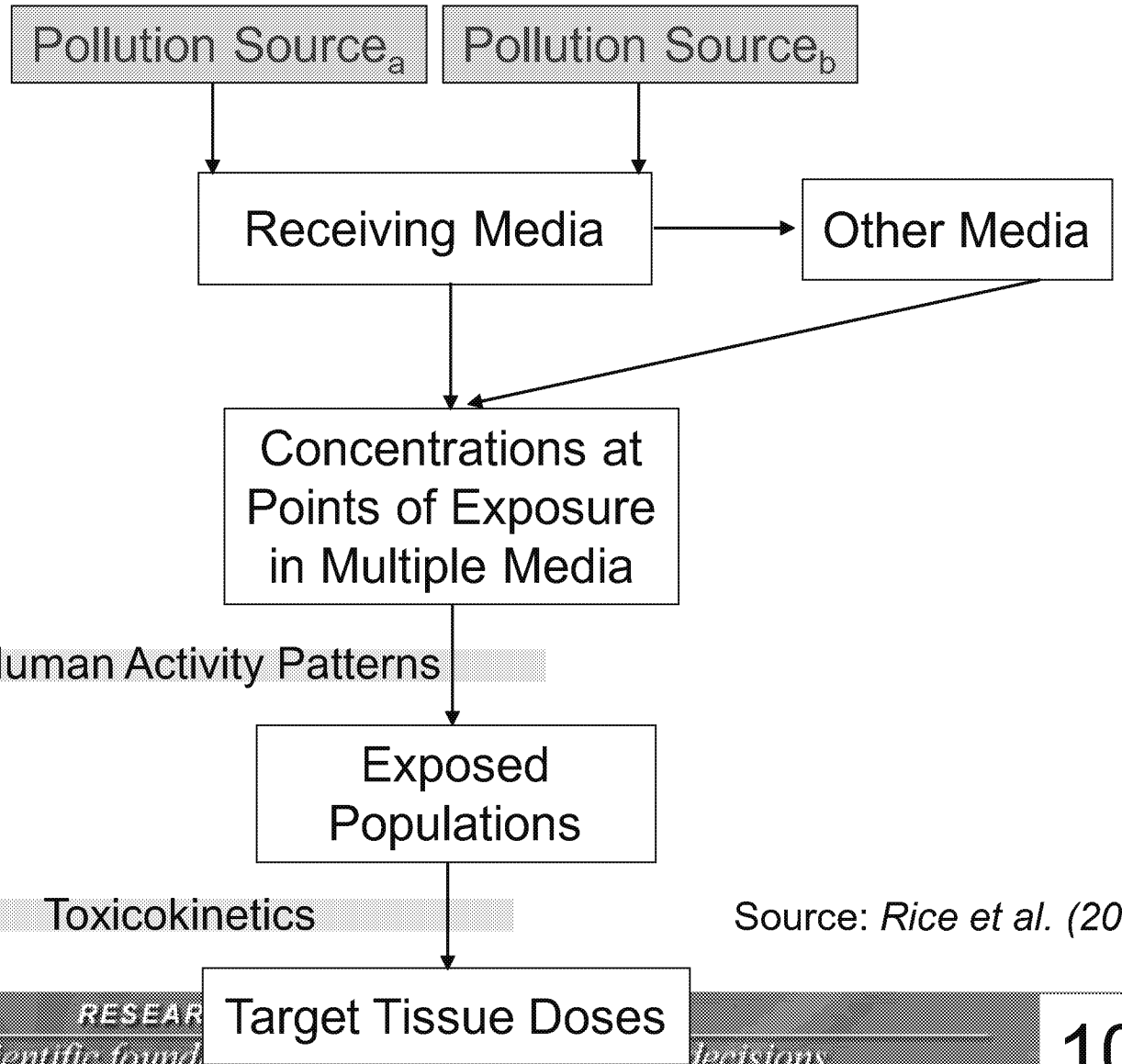
Transformation (degradation)
mediated by biological, chemical, physical agents

Changes can affect composition and toxicity of mixture



Source: *Rice et al. (2008)*

MIXTURE EXPOSURES



Humans exposed concurrently and sequentially to many chemicals

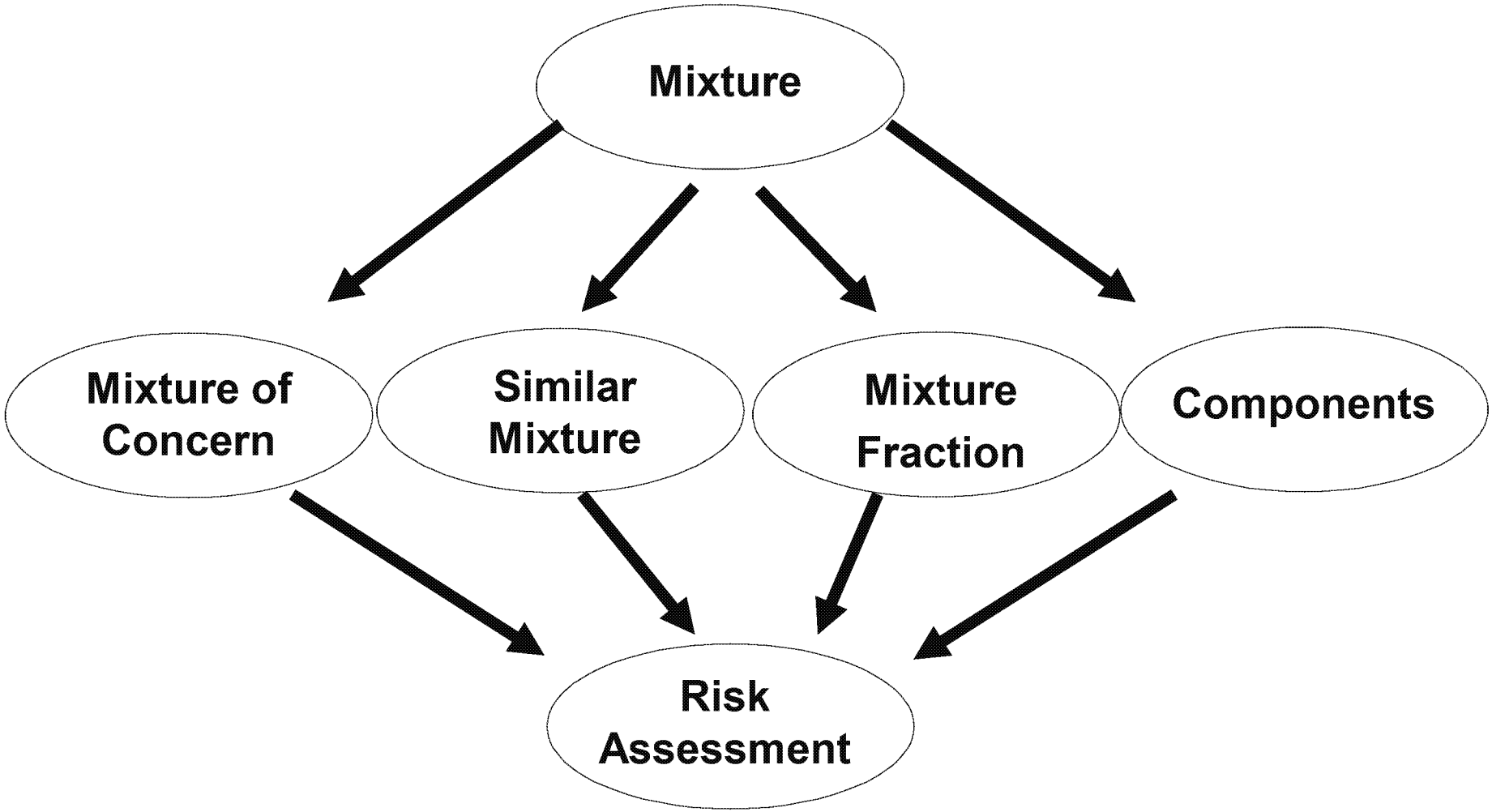
- various routes of exposure
- over varying periods of time

Primary exposure routes:

- ingestion
- dermal absorption
- inhalation

Source: *Rice et al. (2008)*

Chemical Mixtures Health Risk Assessment: Approaches



Choice of approach is data-driven

Component Methods

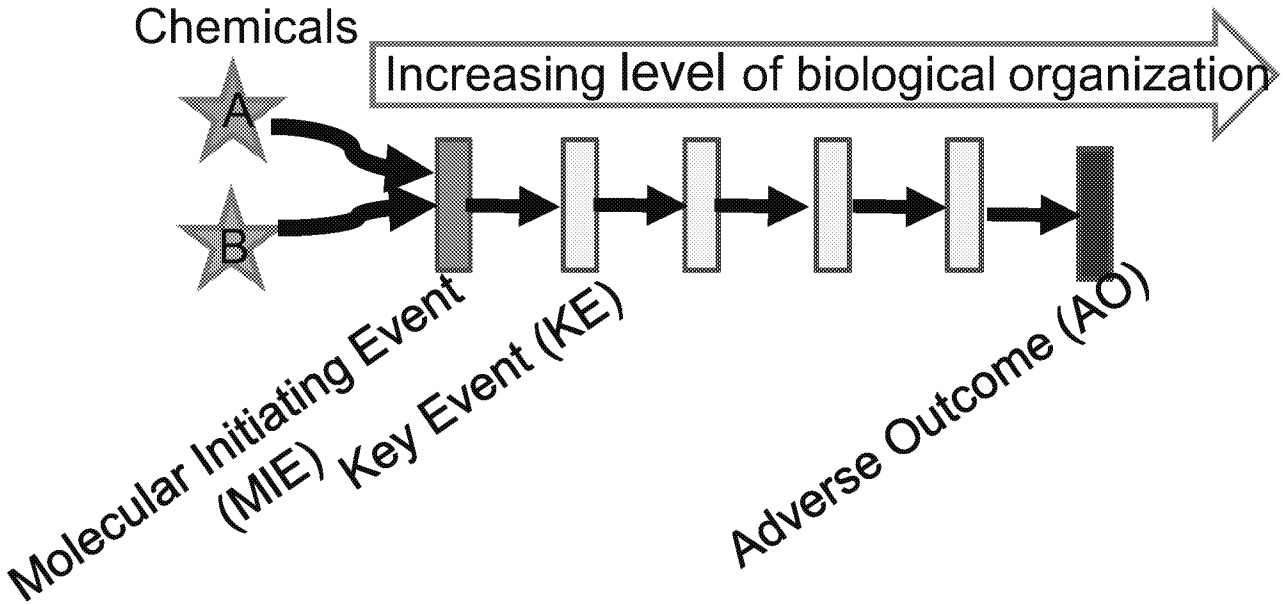
Based on 1 of 3 Assumptions regarding Joint Toxic Action

1. **Simple Similar Action**
2. **Simple Dissimilar Action**
3. **Toxicological Interaction**

ADDITIVE JOINT TOXIC ACTION: SIMPLE SIMILAR ACTION

Dose addition: hazard index (HI), toxicity equivalence factors (TEFs), relative potency factors (RPFs)

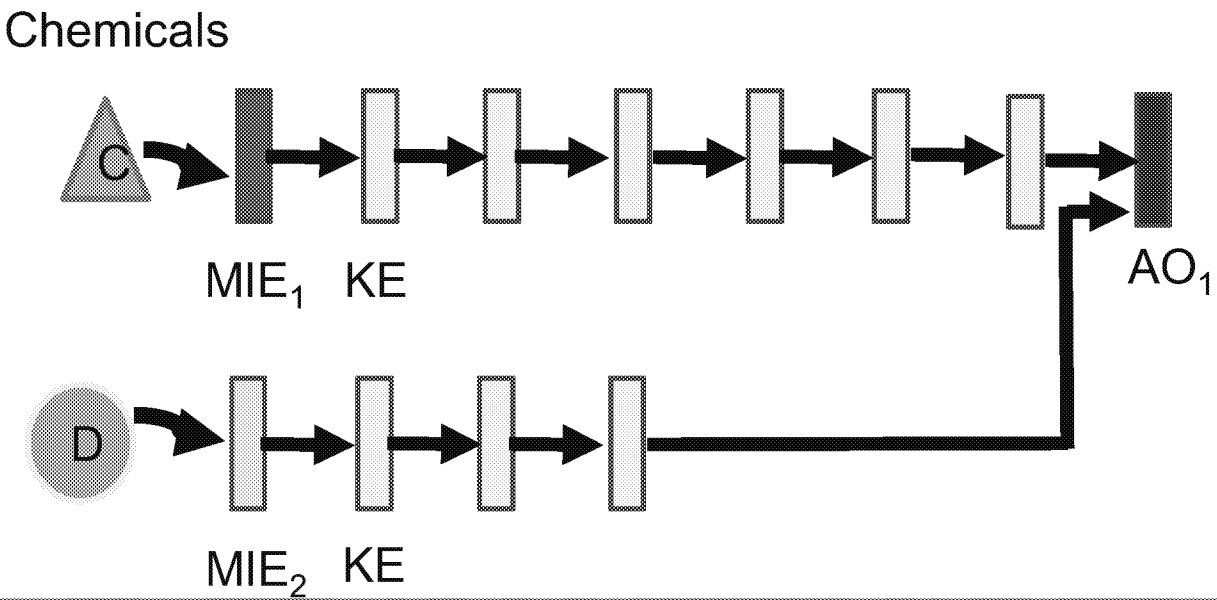
- Addition of component doses, scaled for relative toxicity
- Assumes components affect same pathway of toxicity



Mixture of 2 chemicals, Chemical A and Chemical B, act as toxicodynamic clones, affect same adverse outcome thru same mode of action; doses add at the MIE in this hypothetical AOP

ADDITIVE JOINT TOXIC ACTION
SIMPLE DISSIMILAR ACTION

- Response addition—cancer risk sums
  - Addition of component risks
  - Assumes toxicological and statistical independence
- Effects addition—cumulative effects
  - Addition of biological responses across components
  - Assumes toxicologic similarity across components



Mixture of 2 toxicologically independent chemicals affect same adverse outcome thru different pathways

TOXICOLOGICAL INTERACTIONS

- Toxicologic interactions
  - Defined here as any toxic responses that are greater than or less than those observed under the specified type of additivity, including new responses (not observed when chemicals dosed individually)
- Interaction effects
  - Many applicable terms (e.g., inhibition, masking, etc.)
  - Most common terms refer to descriptor that are:
    - greater than additive (i.e., synergism)
    - less than additive (i.e., antagonism)
- Interaction-Based Hazard Index Method

Hertzberg, R.C.; MacDonell, M.M. Synergy and other ineffective mixture risk definitions. *Sci. Total. Environ.* **2002**, *288*, 31–42.

Dose-Addition: Hazard Index

$$HI = \sum_{i=1}^{n} \frac{Estimated\ Intake_i}{RfV_i}$$

Interpreted as an indication of potential risk when HI > 1

- Scaling factor = (1 / RfV_i) for each chemical *i, where i = 1,2…,n*
- RfV_i is a Reference Value, allowable intake for sensitive humans [e.g., oral Reference Dose (RfD) for chronic oral exposures]
- Estimated Intake (same units as RfV_i)
- Common MOA relaxed to same target organ
- Use at low exposures where interaction effects are unlikely

- Note: other benchmarks can be used instead of an RfV but these typically represent an effect level (e.g., BMDL or LOAEL) from a toxicology study so the HI for humans is underestimated
- Often used as an initial screen

US EPA, 2000

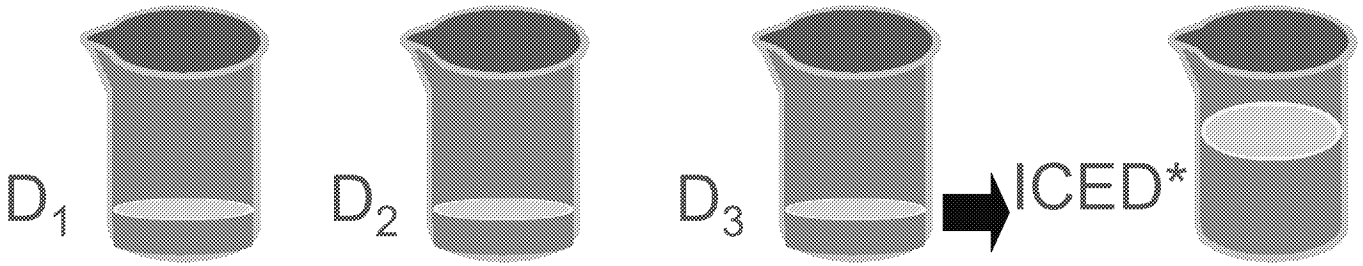
Example Hazard Index Calculations

Chemical	Intake (mg/kg/d)	RfD (mg/kg-d)	HQ Intake/ RfD	% Total Intake	Toxicity Target	UF
Arsenic	3.00E-04	3.00E-04	1.0	4.4	Dermal	3
Chlordane	9.00E-05	5.00E-04	0.2	1.3	Liver	300
Dieldrin	1.00E-04	5.00E-05	2.0	1.5	Liver	100
Lindane	4.00E-04	3.00E-04	1.3	5.8	Liver	1000
Methoxychlor	6.00E-03	5.00E-03	1.2	87.1	Reproductive	1000
	6.89E-03			100		

	Dermal	Liver	Repro	Total
Hazard Index	1	3.5	1.2	5.7

Risk Characterization/Uncertainty Analysis: HI for the liver clearly drives the risk; most toxic chemical, dieldren, is important but only 1.5% of total intake. Reproductive HI is > 1 but large UF used to derive the RfD makes this result uncertain; however, methoxychlor is 87.1% of total intake, also making this chemical a concern. Arsenic HQ = 1, with small UF=3, so Dermal HI is of concern, even though numerically marginal. Variation and uncertainty in exposure intakes is unknown here and could have an impact on the true values of the HI.

Dose Addition: Relative Potency Factors (RPFs) Generalized Index Chemical Method



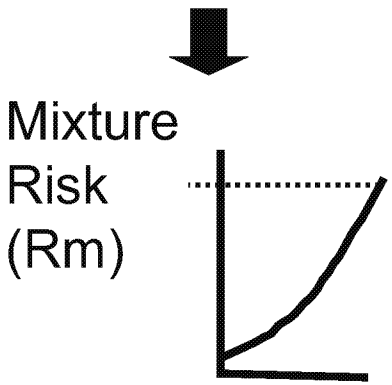
Dose Addition:
Assumes common mode of action

RPF Method

$Rm = f_1(D_1 + RPF_2D_2 + RPF_3D_3) = f_1(ICED)$

where RPF_i scales the doses of chemicals 2 and 3 for relative potency to index chemical 1

*ICED = Index Chemical Equivalent Dose



Index Chemical 1's Dose Response Curve

Methods to Calculate RPFs

For mixture components, chemical i and index chemical 1, the Relative Potency Factor (RPF_i) may be estimated as:

1) the ratio of equally toxic doses of the 2 chemicals, e.g.,

$$RPF_i = \frac{ED_X\left(Index\ Chemical\right)}{ED_X\left(Chemical_i\right)}$$

ED_x = The "Effective Dose" at which an x% response is observed.

2) the ratio of potency factors of the 2 chemicals, e.g.,

$$RPF_i = \frac{Dose\ Coefficient\left(Chemical_i\right)}{Dose\ Coefficient\left(Index\ Chemical\right)}$$

Formula for the Index Chemical Equivalent Dose (ICED)

RPF formula for expressing the mixture dose for *n* chemicals in terms of the index chemical:

$$ICED = \sum_{i=1}^{n} \left[RPF_i \, X \, D_i \right]$$

where,

ICED = mixture dose expressed as dose of the index chemical

D_i = dose of the *i* th mixture component (*i* = 1,…,*n*), and

RPF_i = toxicity proportionality constant relative to the index chemical for the *i* th mixture component (*i* = 1,…,n).

Choice of Index Chemical

- Well studied with well characterized dose-response function for effect of interest
- Toxicologically similar to other chemicals in group
- Chemical properties similar to other chemicals in group
- Confirmation of effects in humans, if data exist
- Data available to compare relative toxicity between index chemical and other chemicals in group
- Confidence increases if typically found in large percent of environmental concentrations as compared with other chemicals in group

RPF Example: Toxicity Data for a Four Chemical Mixture

Chemical	Study ED_{10} (mg/kg/day)	Test Species	Duration Critical Study	Overall Data Set Characteristics
Chemical 1	5	Rat	90 days	Poor. Few poor studies.
Chemical 2	25	Rat	90 days	Extensive. Human confirmation of effects, strong evidence of dose-response
Chemical 3	40	Rat	90 days	Good. Many good studies, many endpoints, multiple species. Some Dose-response data.
Chemical 4	100	Rat	90 days	Limited. Few well-conducted studies.

RPF values for a set of chemicals could differ depending on the effect of interest.

RPF Example: Calculation of RPFs and ICED

Chemical	Rat ED_{10} Oral (mg/kg/d)	RPF (oral dose)	Human Intake (mg/kg/d)	ICED (mg/kg/d)	Total ICED (mg/kg/d)	% of Total ICED
Chemical #1	5	5.0	0.002	0.01		91
Chemical #2 Index Chemical	25	1.0	0.0007	0.0007	0.011	6
Chemical #3	40	0.625	0.0004	0.00025		2
Chemical #4	100	0.25	0.0002	0.00005		1

$RPF = ED10_{IC} \div ED10_{i}$

ICED = RPF × Human Intake

RPF Example: Cancer Risk Estimate Using ICED when Index Chemical is analyzed using a Linear Non-Threshold Model

Index Chemical Comparison	Total **ICED = 0.011** (mg/kg-d) Conduct Assessment Using **Index Chemical Dose Response Information**	Potential Risk
Cancer Risk for the Mixture (Rm)	Oral Slope Factor = 6.2×10^{-2} per mg/kg-d (liver tumors) $Rm = 0.011 \times 6.2 \times 10^{-2}$	Rm = 6.8×10^{-4}

RPF Example: Noncancer Single Oral Route Hazard Estimates Using the ICED

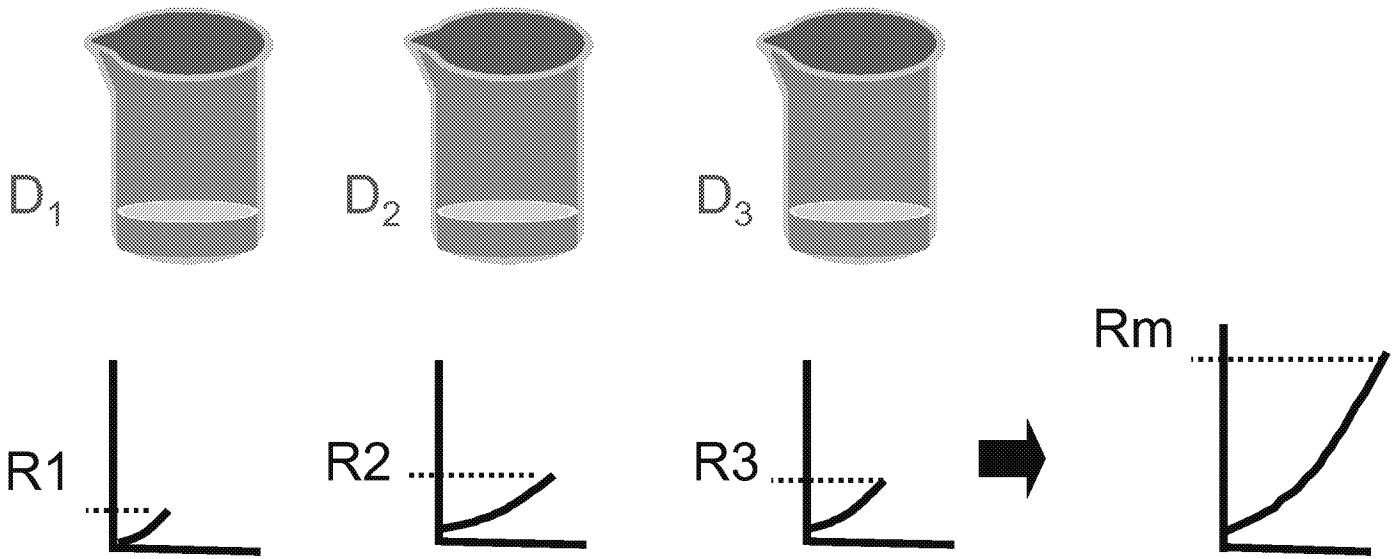
Index Chemical (IC) Comparison	Total **ICED = 0.011** (mg/kg-d) Conduct Assessments Using **Index Chemical Dose Response Information**	Potential Hazard
Hazard Quotient (HQ) for the Mixture	Reference Dose = 0.02 mg/kg-d (renal cytomegaly; UF=100) HQ = **0.011** ÷ 0.02	HQ = 0.55

HQ is ratio of Human mixture exposure to level of the Index Chemical. HQ<= 1 is likely to be without an appreciable risk of deleterious health effects over a lifetime; HQ>1 is of concern.

Comparison of TEFs and RPFs

Toxicity Equivalence Factor Specific Type of RPF	Relative Potency Factor Generalized Case
All health endpoints	May be limited
All routes	May be limited
All timeframes of exposure	May be limited
Encompasses all doses	May be limited to specific dose range
Implies more abundant data are available	May be based on lower quality/ fewer data
Implies greater certainty about mechanism of action	Assumes similar mode of action May be more accurate because application can be constrained given available data
One TEF set for all scenarios	Can generate different RPF sets for various scenarios

Response Addition: Applied Extensively to Estimate Mixture Risk (Rm) for Carcinogens



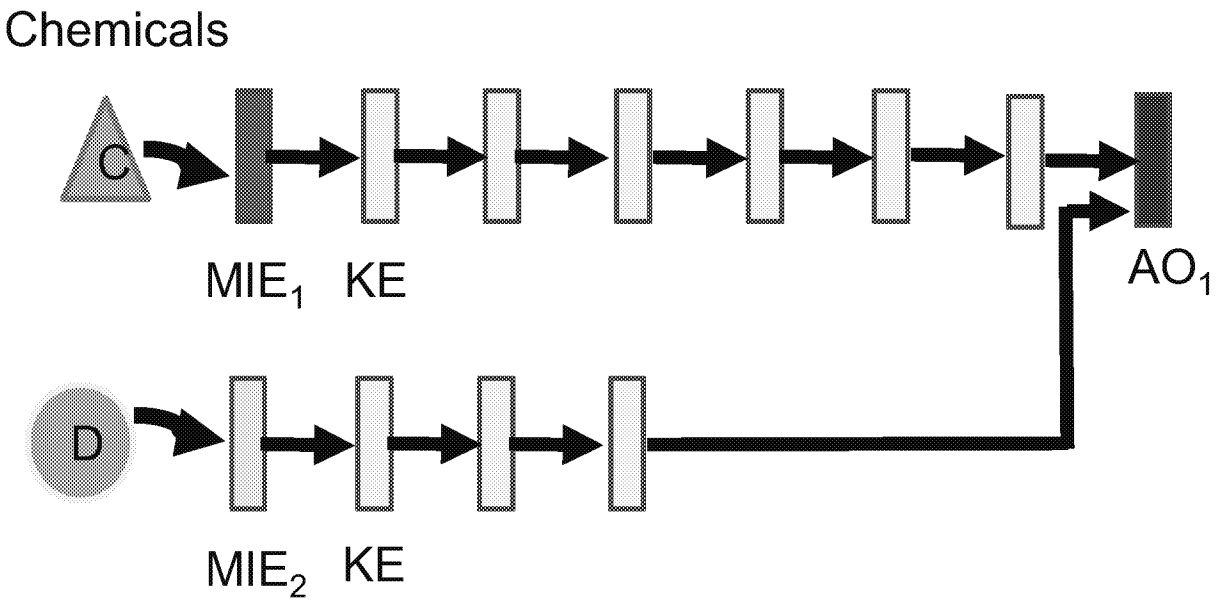
Response Addition: Independence of Toxic Action

$Rm = f_1(D_1) + f_2(D_2) + f_3(D_3) = R_1 + R_2 + R_3$

For a common health outcome, the toxicity caused by the first chemical has no impact on the toxicity caused by the second chemical (and so on for more chemicals).

Response Addition

- Addition of component risks
- Assumes toxicological and statistical independence



Mixture of 2 toxicologically independent chemicals affect same adverse outcome thru different pathways

Response Addition Example
Calculations for Oral Cancer Risk

Chemical	Unit Risk (per µg/L)	Intake (µg/L)	r_i	Organ	Class
Arsenic	5.00E-05	3.00E-04	1.5E-8	Dermal	Carcinogen
Chlordane	1.00E-05	9.00E-05	9E-10	Liver	Likely
Dieldrin	4.60E-04	1.00E-04	4.6E-8	Liver	Likely
Heptachlor	1.30E-04	6.00E-03	7.8E-7	Liver	Likely
Hexachloro-benzene	4.60E-05	4.00E-03	1.8E-7	Liver	Likely
Total Excess Lifetime Cancer Risk per the Exposure =			1.E-6		

Assumes Toxicological and Statistical Independence

Uncertainties: EPA's Integrated Risk Information System (IRIS) data are 95% upper bound slope factors; Most of the risk is from chemicals with a cancer weight of evidence descriptor of "likely to be carcinogenic in humans", as opposed to being designated a "human carcinogen"; Toxicological independence is uncertain, given that the primary target organ contributing to risk is the liver.

Fraction Method

Total Petroleum Hydrocarbon (TPH) Release Sites

Petroleum release sites include:

- Active and abandoned waste sites
- Facilities/properties where fuels are stored, distributed, or sold
  - Government sites
  - Private sector sites
- Sites where fuel storage tanks have leaked

Problem:

- Increased cancer risks and non-cancer effects (e.g., renal, breathing and neurological problems) associated with increased exposures to petroleum hydrocarbons and hydrocarbon fractions
- Petroleum release sites risk assessments pose complex and unique challenges

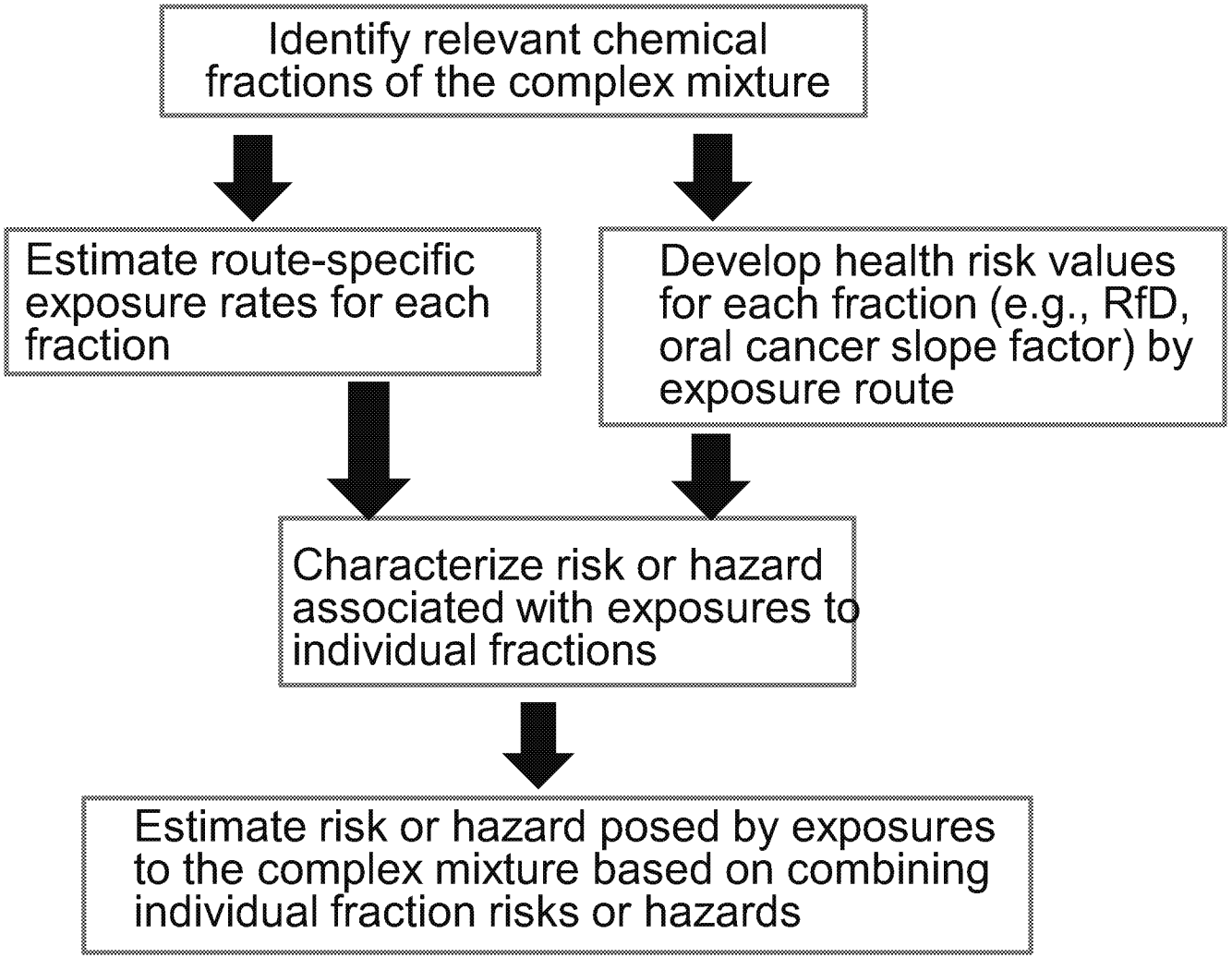
Adapted from Interstate Technology and Regulatory Council (ITRC) TPH Risk Evaluation at Petroleum-Contaminated Sites, 2018; US EPA, 2009

Total Petroleum Hydrocarbon (TPH) Background

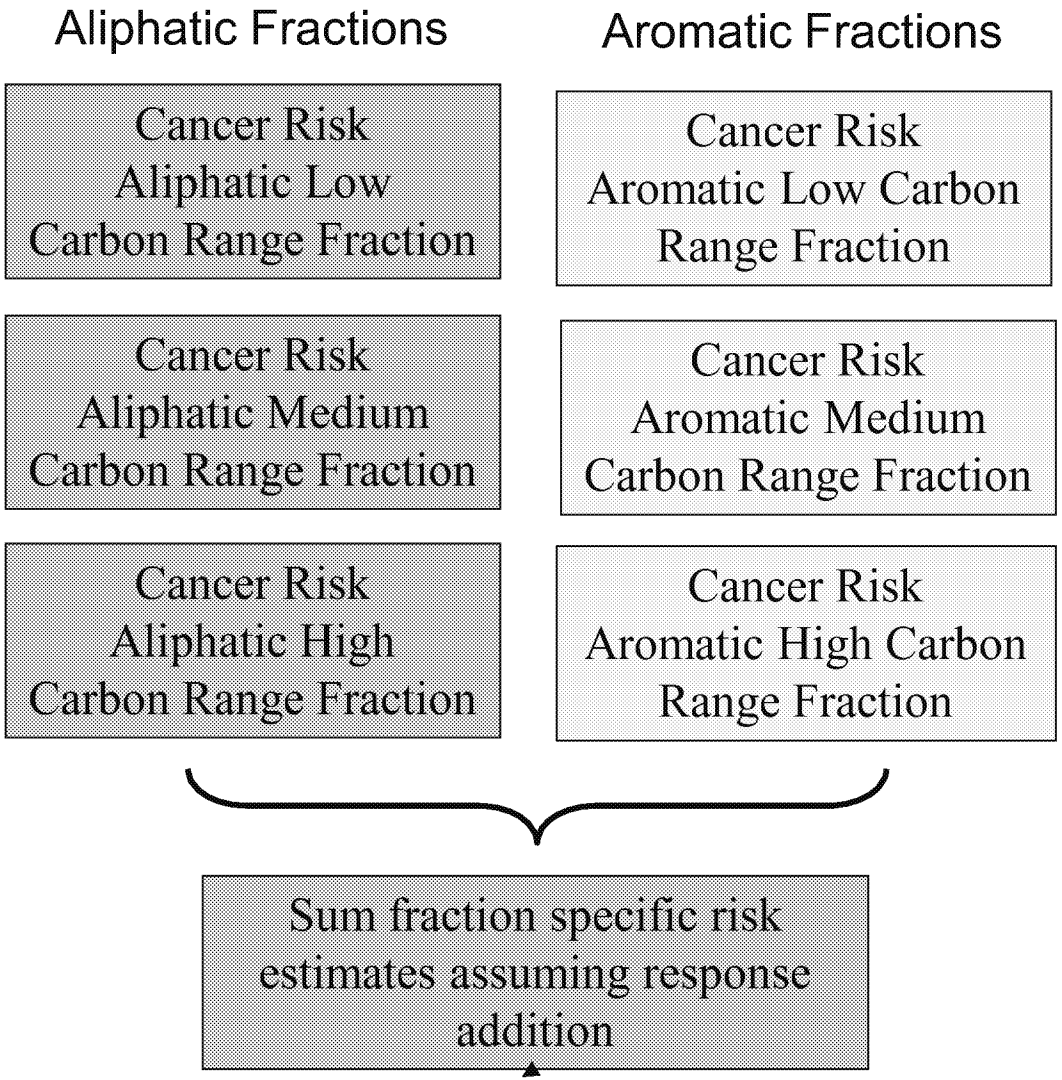
- TPH Exposures: Unique Considerations
  - Differences in composition of released fuels
  - TPH occurrences can exhibit spatial and temporal variability due to differential fate of components, including:
    - transport through individual compartments
    - partitioning among compartments (soil, water, and air; abiotic and biotic),
    - petroleum metabolites - transformation (degradation) mediated by biological, chemical, physical agents
  - Lead to different toxicities
  - Different analytical methods

- Human TPH exposures can occur through different environmental media (e.g., soil, water, air), different activity patterns, and 3 different exposure routes (dermal absorption, ingestion, inhalation)

General Fraction-Based Approach for Evaluating Risks or Hazards associated with Complex Mixtures



Overview: Total Petroleum Hydrocarbon (TPH) Fraction Approach



EPA, 2009. Provisional Peer-Reviewed Toxicity Values for Complex Mixtures of Aliphatic and Aromatic Hydrocarbons.

Whole Mixture Methods

Whole Mixture Methods

- Risk assessors generally have more confidence in assessments based on whole mixture methods than those based on component methods
- Generally there are fewer data on whole mixtures
- Applicability concerns, because composition of tested mixture may differ from environmental mixture

Some Sources of Whole Mixtures

- Emissions from fixed sources (industrial emissions, municipal incinerators) and mobile sources (cars, planes)
- Releases from engineering processes (drinking water disinfectant byproducts)
- Sources/releases related to lifestyles (food, smoking, sprays, fuels, botanicals)
- Contaminated environmental media (indoor air, outdoor air, fish tissue, soil at Superfund Site)
- Occupational process-related releases (workplace dusts)
- Product applications (pesticides and herbicides)
- Degradation processes (weathering of pesticides)

Evaluating Complex Mixtures: Which Mixture toTest?

- Actual environmental mixture
- Environmental mixture similar to the one of concern in the environment
- Lab concoction generated by a similar process
- Fractions of whole mixture
- A created, defined mixture of key chemicals, or
- A single key chemical

Each of these approaches has been used in environmental human health risk assessments

Increasing the Relevance of Toxicological Testing of Complex Mixtures to Risk Assessment

1) Test near current human exposure levels, generally in low response region*
2) Test proportions of component chemicals similar to those measured in environmental samples
3) Include unidentified components (i.e., unknown components that may comprise a fraction of the mixture) in tested mixtures

*While hazardous chemical concentrations in environmental and exposure media (in many countries) are low (correspond to low response regions of dose-response curves), chemical concentrations in occupational settings and in environmental media following accidents/disasters can be quite high.

Source: Teuschler et al., 2002; Simmons et al., 2004, 2008

Procedure to Derive Whole Mixture Toxicity Values

1. Collect and evaluate data
   - Epidemiology/human data preferred to in vivo and in vitro toxicology data
2. Evaluate stability of the mixture
   - Variability in components and their relative proportions
     - Over time within a medium (could be a testing medium or environmental medium)
     - Across media (e.g., uptake and retention of dioxin like congeners: air → plant → beef)
3. Decide which mixture to test (if examining an assortment of comparable mixtures)
4. Conduct dose-response assessment
   - Use single chemical procedures (e.g., RfD, slope factors)
5. Characterize uncertainties
   - Relevance of observed health effects in the study to environmental exposures
   - Stability of the mixture composition (proportions and chemical concentrations) and dose over time. Changes that result from environmental fate as they could affect health outcomes

Source: U.S. EPA, 2000

Whole Mixture Reference Dose (RfDm)

$$RfD_m = \frac{NOAEL,\ LOAEL\ or\ BMDL}{UF_m} X$$

Where:

RfD = Reference dose

NOAEL/LOAEL = No/lowest-observed-adverse-effect level

BMDL = Lower 95% confidence limit on an X% effective dose (e.g., ED_{10})

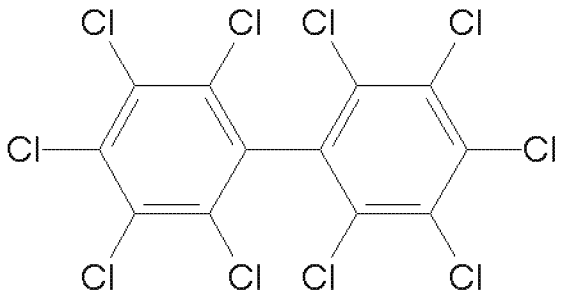
UF_m = Uncertainty factors for the mixture (e.g., interspecies, intraspecies, exposure duration, NOAEL to LOAEL, database deficiencies)

NOAEL, LOAEL or BMDL typically from experimental toxicity data on complex mixture dose-response

Reference Dose "an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime."

Polychlorinated Biphenyls: Background

- 209 PCB congeners
  - Widely varying chemical properties among congeners
  - Different PCB mixtures share components
  - Variable number of chlorines on PCBs

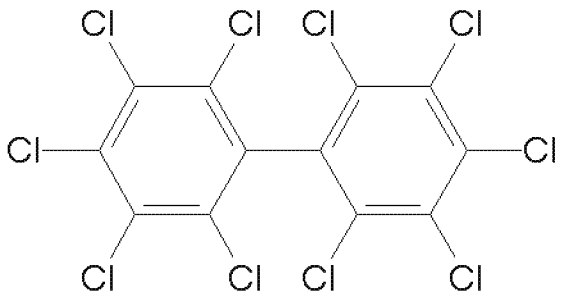


- Reference compounds: 4 Aroclors
  - Commercial PCB mixtures with different levels of chlorination
  - Toxicological evaluations show that the 4 Aroclors have different cancer potency estimates
- Environmental processes alter the cancer potential of PCB mixtures

Source: Cogliano, 1998

Polychlorinated Biphenyls: Bioassay

- EPA identified the low-dose group [received 0.007 mg/kg-day aroclor 1016] as no-observed-adverse-effect level (NOAEL) for mixture.
  - Based on several reports of reproductive studies in monkeys, U.S. EPA (1996) published RfDs for several commercial PCB mixtures, known as aroclors.
  - Aroclor 1016 administered to adult female monkeys beginning 7 months prior to breeding and continuing until offspring weaned at age 4 months.
  - Relative to control animals, birth weights significantly decreased in offspring of the high-dose group that received 0.028 mg/kg-day of aroclor 1016
  - NOAEL is 0.007 mg/kg-day.

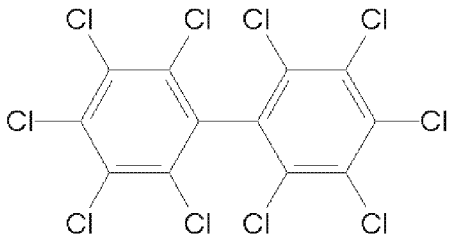


RfD Calculation: Polychlorinated Biphenyls: Aroclor 1016

$$RfD_m = 7E-5 = \frac{NOAEL = 0.007\,mg/kg-day}{UF_m = 100}$$

NOAEL = Reduced birth weight in monkey reproductive study

UF_m = 3 for animal to human extrapolation
3 for general population to a sensitive population
3 for subchronic-to-chronic exposure duration
3 for missing 2 generation repro and adult male repro studies



(UF_m = 100 = 3 × 3 × 3 × 3)

Uncertainty factors are based on a log scale. Factors of 3 are actually 3.16. (The actual value is $10^{0.5}$).

Confidence in RfD is medium. Mix of PCB congeners in the environment do not match those in Aroclor 1016. For environmental applications where it is known that Aroclor 1016 is the only form of PCB contamination, use of RfD may rate high confidence. For all other applications confidence is medium. Source: U.S. EPA's IRIS Database, Accessed 2015

Issues: Complex Mixture Assessment

- Resource intensive
  - Preparation and stability of the complex mixture
  - Chemical characterization
  - Toxicity/Epidemiology studies on complex mixtures
- Limited numbers of complex mixtures can be tested
  - EPA's 4-Lab study analyzed 1 drinking water (Simmons et al., 2004, 2008; Pressman et al., 2010; Narotsky et al., 2012)
- Knowledge of the composition of the mixture
  - Mixture released to environment may differ substantially from mixture encountered in environment (mixtures to which people are exposed)

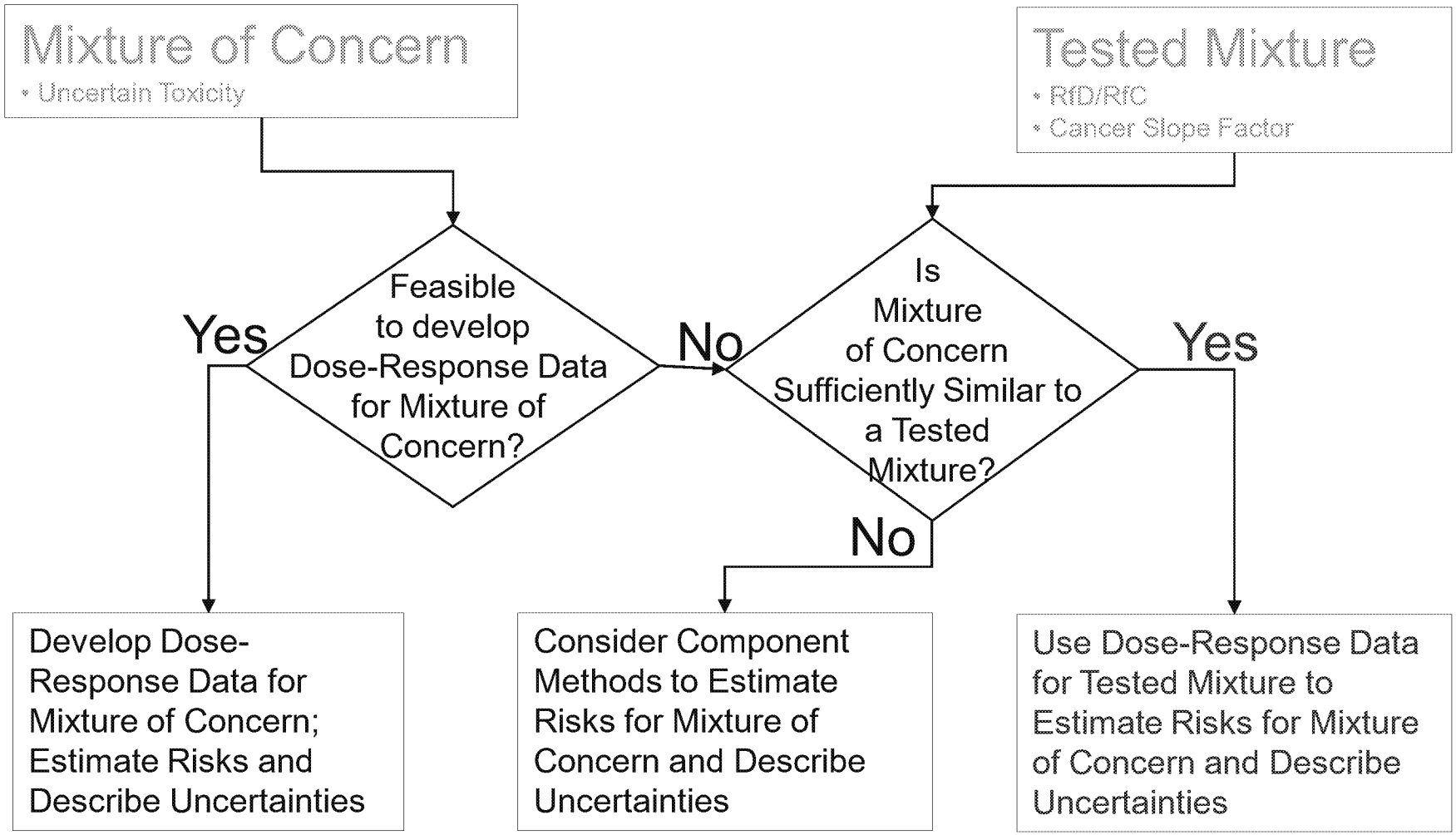
Overview Sufficient Similarity Methods

Sufficient Similarity

EPA 2000 describes general principles, but no methods

- If toxicity data are not available for a mixture of concern, base the risk assessment on a *sufficiently similar* mixture.
- A mixture is sufficiently similar to another when its components are not very different and are in about the same proportions.
- Few differences in environmental fate, uptake, bioavailability and pharmacokinetics.
- Expected toxicological consequences of exposure to the two mixtures are nearly identical.

Sufficient Similarity



Mixtures considered sufficiently similar when expected health consequence of exposure to 2 mixtures nearly identical

Source: US EPA, 2009

Possible Future Directions for Mixtures: Sufficient Similarity

Suf. Sim. methods not described in RAF Guidance

- Opportunity to develop Guidance to determine when other tested mixtures are sufficiently similar to use in risk assessment VS Approaches based testing mixture of concern
  - Some Existing Approaches
    - Feder et al 2009: Evaluates Suf. Sim. using principal component analysis
    - Feder et al 2009 Evaluates suf. Sim. using bootstrap method
    - MIST EPA draft Method & Tool for evaluating Suf. Sim. among PCB mixtures (based on Marshall et al, 2013)
  - Opportunity: Implementing Suf. Sim. approaches based on NAM data

Marshall et al. 2013 "An empirical approach to sufficient similarity: combining exposure data and mixtures toxicology data" Risk Analysis 33(9) 1582-1596

Feder et al., 2009 "Evaluating sufficient similarity for drinking-water disinfection by-product (DBP) mixtures with bootstrap hypothesis test procedures". J Toxicol Environ Health A.;72(7):494-504.

Feder et al 2009. "Evaluating sufficient similarity for disinfection by-product (DBP) mixtures: multivariate statistical procedures." J Toxicol Environ Health A. 2009;72(7):468-81.

Cumulative Risk Assessment

Stressor

- Any physical (e.g., sunlight, heat), chemical, biological (e.g., viruses), or psychosocial entity (e.g., community violence, non-voluntary unemployment) that can induce an adverse response.
  - "Stressor" can include the lack of an essential entity

- Niemeier (2020) distinguished between entities operating through physical pathways (e.g., chemical, biological, or physical entities) and those operating through psychosocial pathways (e.g., perceived stress).

See Niemeier et al., 2020 and references therein

Susceptibility

- Difference in dose-response function in an individual or population relative to another population; for example:
  - different threshold
  - different shaped dose-response function
  - different/additional adverse outcome
- Refers to conditions of differential or heightened responses
  - Response: magnitude of effect measure OR % of population responding
- Increased susceptibility can be due to the following (among others):
  - differences in genetic and epigenetic predisposition
  - health status (e.g., immune-compromised conditions)
  - lifestyle factors (diet, obesity, smoking status, alcohol abuse)
  - age
  - ethnicity
  - sex
  - medications
- Some individuals/populations may be more **resilient.**

See Niemeier et al., 2020 and references therein

Vulnerability

- Difference in exposure (individual or population)
- Refers to condition of differential (e.g., heightened) exposures relative to those experienced by another population.
- Can include differences in historical exposure, body burden, and sources of exposure.

- Here, “vulnerability” used narrowly. Others, e.g., Kasperson, define it more broadly and include differential exposure as one of four categories of vulnerability.

See Niemeier et al. 2020, and references therein

Why Cumulative Risk Assessment?

- Public health officials and ecological risk managers recognized that chemical-focused and source-focused assessments might not comprehensively address the risks experienced by populations.
  - Considering multiple chemical, physical, and biological agents, and psychosocial stressors.
- Many health outcomes of concern, such as cancer and heart disease, were recognized to be multifactorial.
- Questions were raised such as how occupational factors, environmental factors, personal behaviors, genetics, epigenetics as well as life history cumulatively influence health outcomes in populations.

Features of CRA

- Population focus
  - Population vulnerabilities
  - Stakeholder Involvement
- Multiple exposures to chemical, physical, and biological agents, and psychosocial stressors
- Multiple exposure routes/pathways
- Human health and ecology
  - Ecosystem services

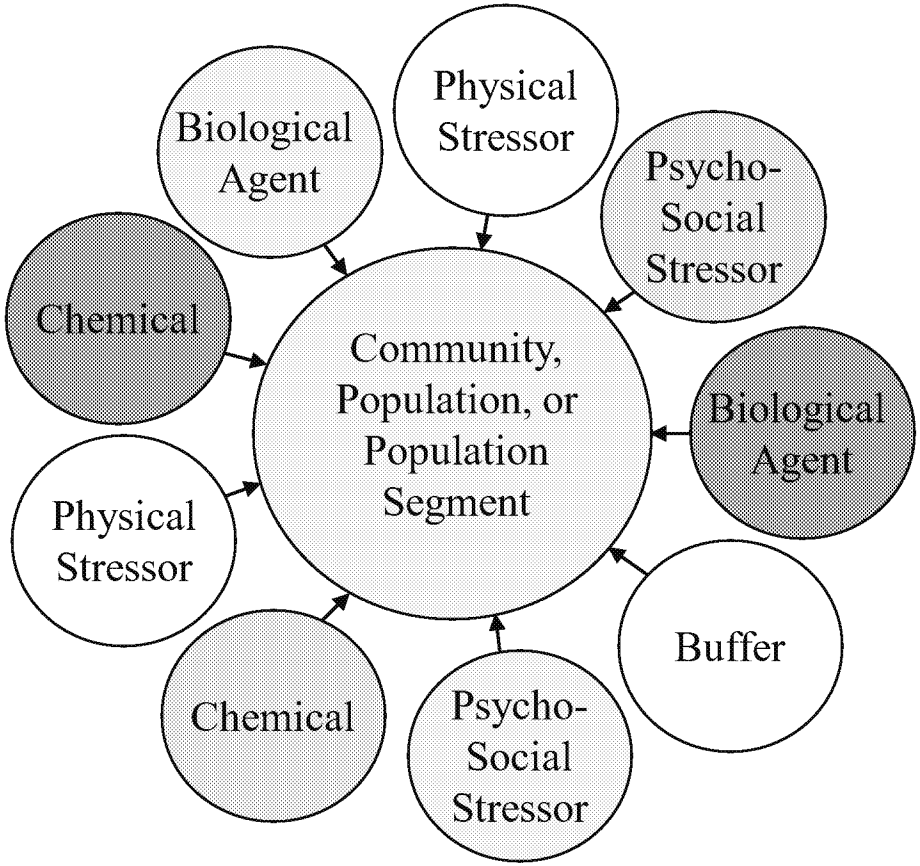


Figure adapted from U.S. EPA, 2003

Defining Cumulative Risk Assessment (CRA)

- Cumulative risk is the combined risks from aggregate exposures to multiple agents or stressors, which may include exposures to chemicals, biological,, or physical agents, and psychosocial stressors
- Cumulative risk assessment is an analysis, characterization, and possible quantification of the combined risks to human health or the environment from multiple agents or stressors
- CRA is population-based with an emphasis on stakeholder involvement

Sources: U.S. EPA. 2003. Framework for Cumulative Risk Assessment. U.S. EPA/ORD/RAF, Washington, DC. EPA/600/P-02/001F. Available at: http://www.epa.gov/raf/publications/framework-cra.htm

NRC (National Research Council). (2009) Science and decisions: advancing risk assessment. Washington, DC: National Academy of Sciences. Available online at http://dels.nas.edu/dels/rpt_briefs/IRA_brief_final.pdf.

NRC (National Research Council). (2008) Phthalates and cumulative risk assessment: the task ahead. Washington, DC: National Academy of Sciences. Available online at http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12528.

Why considering nonchemicals is important

- Synergistic effects for chemical and nonchemical stressors
  - Noise and Solvents
    - Johnson, A. C., and Morata, T. C. (2010). Occupational Exposure to Chemicals and Hearing Impairment. (The Nordic Expert Group), pp. 177. University of Gothenburg, Gothenburg, Sweden. Available at: http://hdl.handle.net/2077/23240.Lead and Chronic Stress

- Differential **Susceptibility** by nonchemicals
  - Chronic psychosocial stress – *susceptible population*
    - Clougherty, Jane E., et al. "Synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology." Environmental health perspectives (2007): 1140-1146
  - Diet – *resilient population*
- Romieu, Isabelle, et al. "Omega-3 fatty acid prevents heart rate variability reductions associated with particulate matter." American journal of respiratory and critical care medicine 172.12 (2005): 1534-1540.

- Differential **Vulnerability** by nonchemicals
  - Socioeconomic status - *Environmental Justice (EJ) population*
- Nelson JW, Scammell MK, Hatch EE, Webster TF. 2012. Social disparities in exposures to bisphenol a and polyfluoroalkyl chemicals: A cross-sectional study within nhanes 2003-2006. Environmental Health 11:1-15.

Non-chemicals

Nonchemical Exposures*

Biological

- Microbes
- Viruses
- Fungi
- Yeast

Physical

- Sound
- Temperature
- Humidity
- Vibration
- Radiation

Psychosocial Stressors

- Community Violence
- Community Crime
- Non-voluntary unemployment
- Natural Disaster

Life situations that create an unusual or intense level of stress

**Lists not intended to be comprehensive*

Biological Agents

Hazard Identification

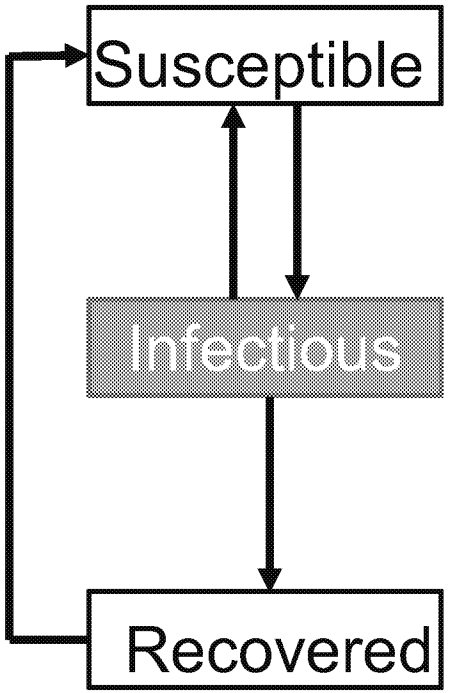
- Human health data, population morbidity

Exposure Assessment

- Quantal measures
- Models for disease spread (e.g., SIR Models)

Dose-response

- Epidemiology studies, often ordinal or quantal



Acceptable levels:

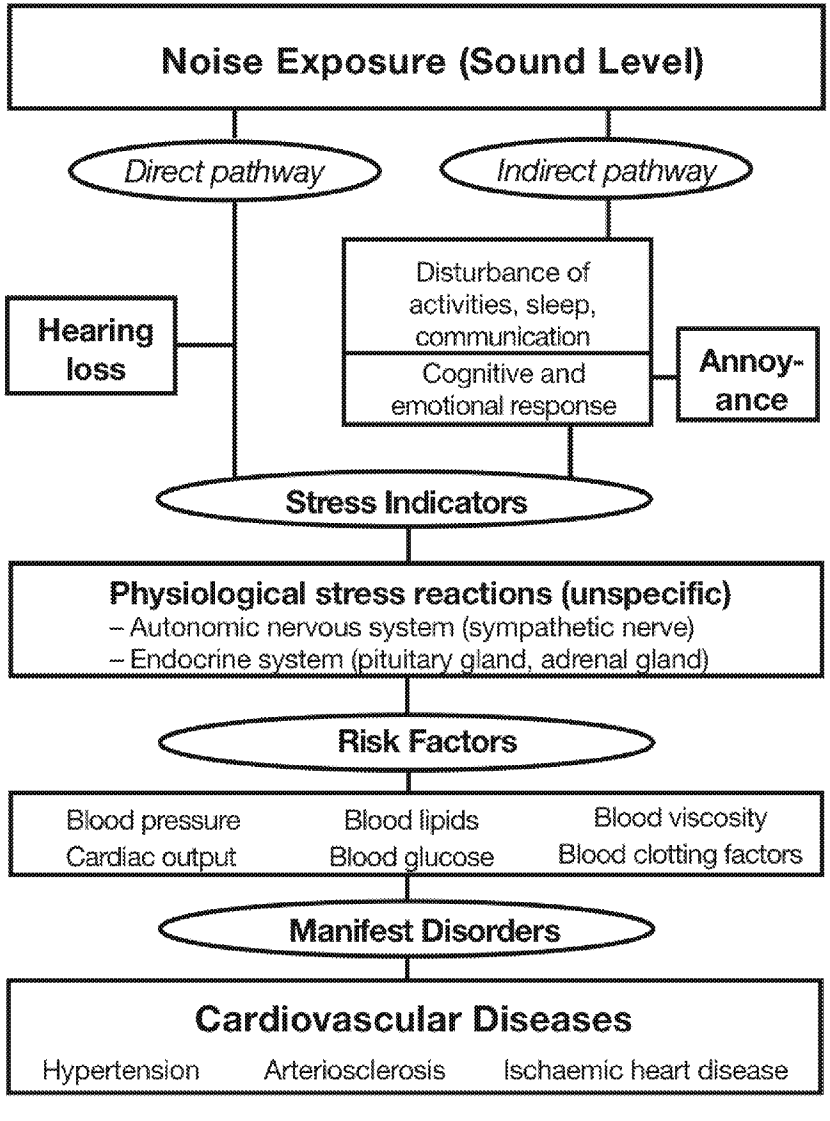
- Few regulations: EPA and World Health Organization (WHO) guidance

Physical Agents

- **Temperature**
  - **Increased body temperatures have the potential to alter absorption, clearance, and toxicity of chemicals in humans.**
- **Physical exertion**
  - **Electrolyte balance** *(Gatorade OD during BP cleanup)*
  - **Joint effect with temperature** *(heart attacks shoveling snow)*
- **Vibration & noise**
  - **Vibration**: direct tissue injury
  - **Sound**: hearing loss (higher than additive effect with joint chemical exposure)
  - **Noise** (as nuisance): sleep deprivation, tension-anxiety

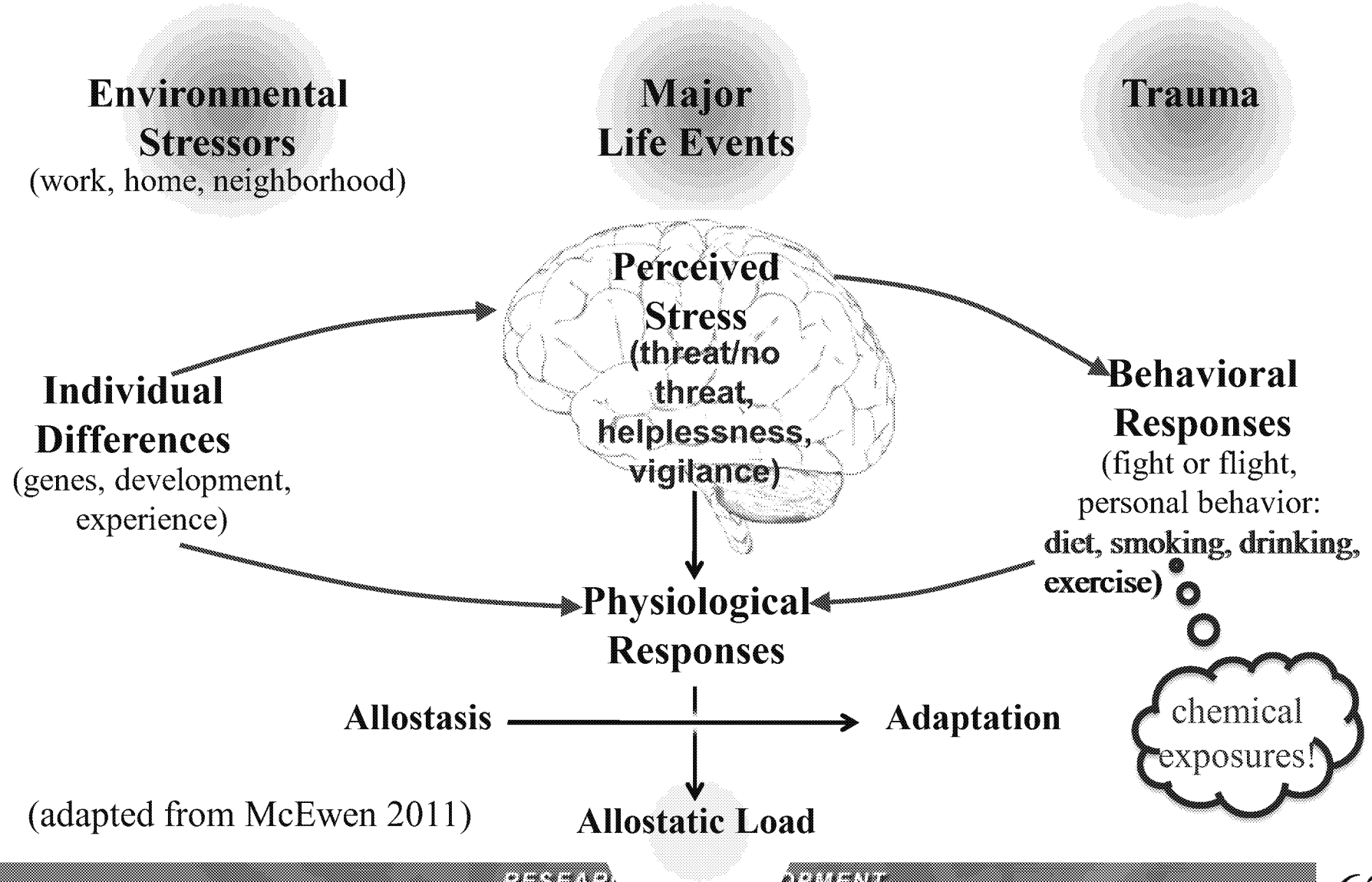
Exposure levels can be measured, some limits exist for workers & public

Physical Stressors: Sound/Noise Conceptual Model



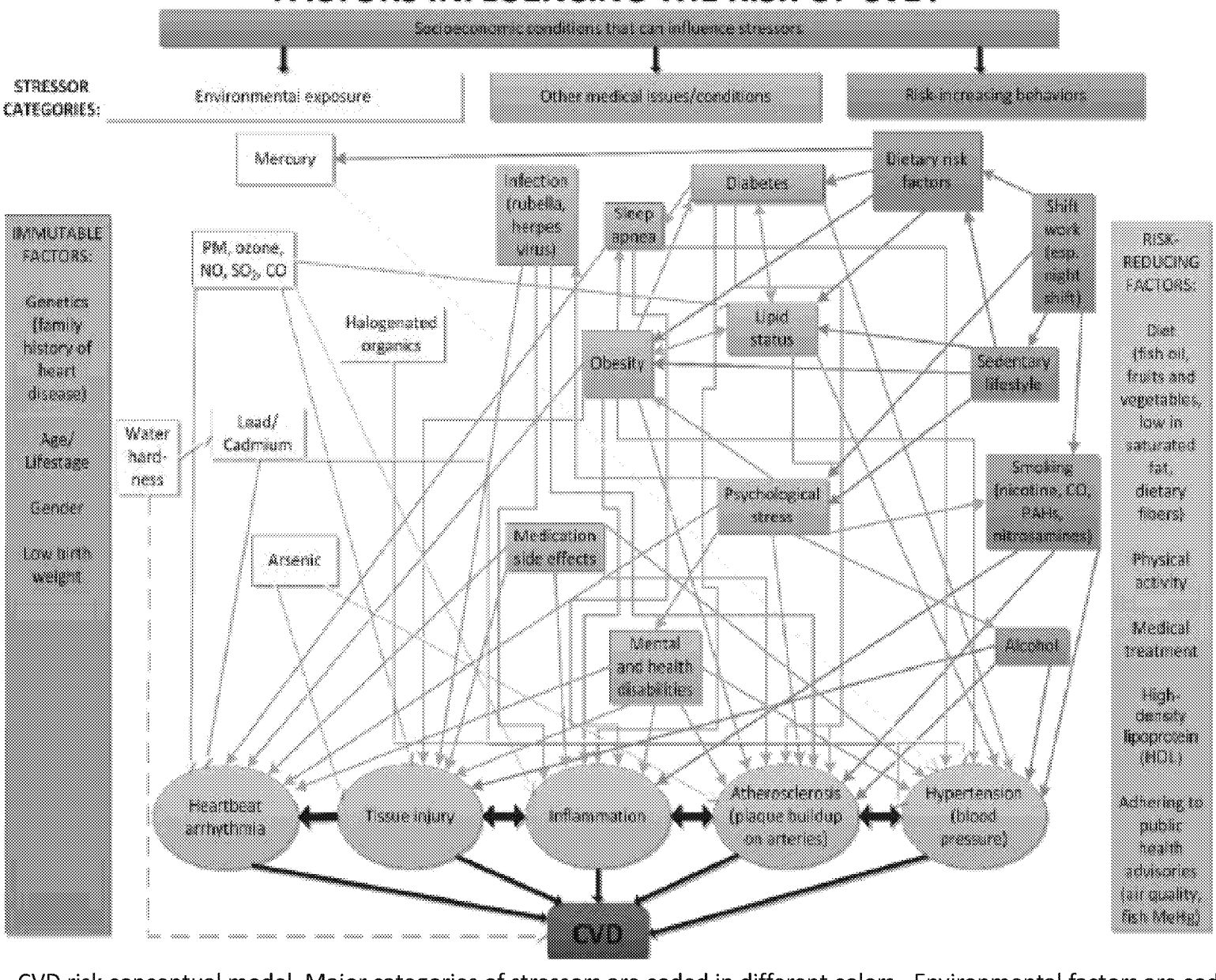
WHO 2009. Night Noise Guidelines for Europe.

Chronic Psychosocial Stress



(adapted from McEwen 2011)

Kashuba, et al., 2021. Risk of cardiovascular disease is driven by different combinations of environmental, medical and behavioral factors: HERA DOI: 10.1080/10807039.2021.1925083



CVD risk conceptual model. Major categories of stressors are coded in different colors. Environmental factors are coded in yellow, medical factors are coded in purple, risk-increasing behaviors are coded in orange, immutable factors are coded in pink, risk-reducing factors are coded in teal, proximal biological mechanisms are coded in peach, and adverse health effect of concern is coded in red.

Cumulative Risk Assessment Summary

- CRA is an analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors
- National Research Council (2012) CRAs could provide a "broader and more comprehensive understanding of the complex interactions between chemicals, humans, and the environment"
- CRA design is specific to the decision it will inform
- CRAs can be a resource-intensive when there are many potentially contributing factors and the risk management outcome is highly consequential.
  - well-defined problem for which a risk characterization is required that integrates several agents or stressors to inform the environmental management decision
  - determine that there are adequate methods, data and resources available to successfully conduct the assessment
  - EPA (2017) suggests following a tiered assessment approach

Supplemental

How Microbes and Chemicals Differ

1. Microbial death and growth
   - Environment and Host; toxins may remain after microbes are gone
2. Host immunity and susceptibility
   - Dynamic models to determine immune status; Concomitant illnesses and medications
3. Diversity of health endpoints
   - Same dose of pathogen may result in a broad range of health outcomes or endpoints depending on the characteristics of the host and exposure scenario
4. Genetic diversity and evolution of microbial strains
   - A "moving-target" because the distribution of strains and virulence factors can fluctuate rapidly in a given medium
5. Potential for secondary transmission
   - Zoonotic transmission; Fomites; Asymptomatic chronic carriers
6. Heterogeneous spatial and temporal distribution in the environment
   - Clustered distribution-clumping; Episodic/Seasonal occurrence

Microbial Risk Assessment Guideline: Pathogenic Microorganisms with Focus on Food and Water (US EPA 2012) http://www.epa.gov/raf/microbial.htm

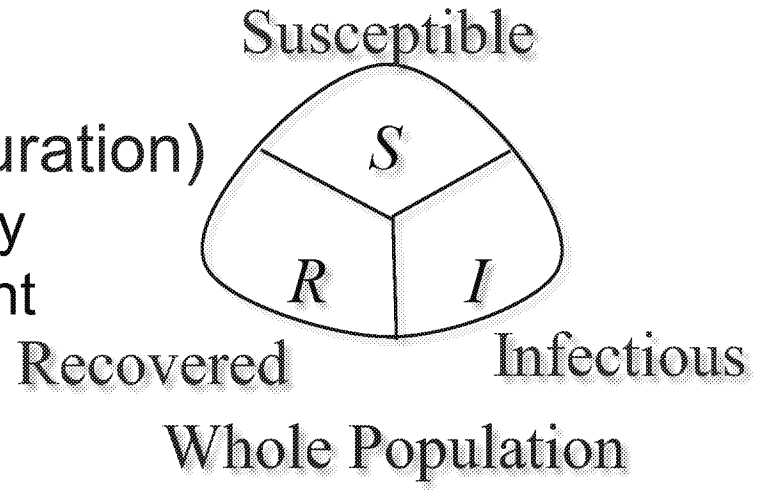
How Microbes are Different from Chemicals cont.

7. Single exposure health outcome
    - Typically, single exposure with health effects noticeable within days/weeks
8. Wide range of microbial response interventions
    - Microbial levels in ambient versus treated drinking water
9. Detection method sensitivity
    - Laboratory detection methods may not be sensitive enough to detect pathogens at a level of regulatory concern
        - A single pathogen could transmit infection
10. Population, community, and ecosystem-level dynamics
    - Pathogens compete with nonpathogens for resources
    - Many nonviral human pathogens have animals hosts
11. Routes of exposure
    - Direct person-to-person or person-to-environment-to-person
        - Primary and secondary host transfer can differ

Microbial Risk Assessment Guideline: Pathogenic Microorganisms with Focus on Food and Water (US EPA 2012) http://www.epa.gov/raf/microbial.htm

What are the Risk Management Goals?

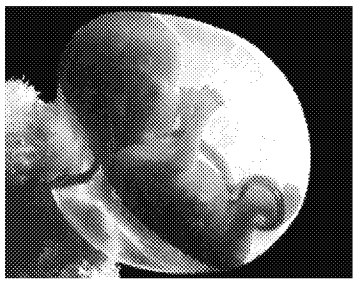
- Limiting **chance** of disease
  - Risk per person?
  - Exposure in multiple locations? How is exposure measured?
- Mitigating **effects** (severity, duration)
  - Enhancing treatment availability
  - Reducing time to start treatment
  - Prophylaxis
- Controlling **spread** of disease
  - Number of locations? Size of each population?
  - Specific locales? (e.g., hospitals, sports events, schools)



Cumulative Exposure to Neurodevelopmental Stressors in Women of Reproductive Age: NHANES 2003-2004

Source: Evans, A.M., G. E. Rice, L.K. Teuschler, and J. M.Wright. 2014. Joint Exposure to Chemical and Nonchemical Neurodevelopmental Stressor Hazards in U.S. Women of Reproductive Age in the 2003−2004 NHANES: An Exploratory Analysis. Int. J. Environ. Res. Public Health 2014, 11, 4384-4401; doi:10.3390/ijerph110404384 http://www.mdpi.com/1660-4601/11/4/4384

Neurodevelopmental Toxicity (NDT)



- **Fetal neurodevelopment** is a critical window of vulnerability to many stressors
- **Neurodevelopmental stressors**
  - **Chemicals**
    - Lead (Pb) (Lanphear et al., 2005)
    - Methyl mercury (MeHg) (Grandjean et al., 2012)
  - **Non-chemical**
    - Maternal stress (Bergman et al., 2010)
  - **Maternal stress modifies lead-induced NDT** (Cory-Slechta et al., 2004)

Study Aims

1. Characterize joint exposure to chemical (**Pb and MeHg**) and **chronic stress**

2. Identify potential maternal populations that are more likely to be exposed to NDT hazards

Quantifying Chronic Stress: Allostatic Load (AL)

- **Allostasis** is defined as "maintaining stability through change" (Sterling & Eyer, 1988)
- **Chronic stress** may result in physiological dysregulation (McEwen & Wingfield, 2003)
  - Physiological dysregulation **taxes the body** and has been measured using the concept of allostatic load (AL)
- AL can be operationalized as the **sum of "elevated" physiological parameters**
  - Elevated physiological parameters are **secondary mediators** to elevated cortisol in response to stress

Methods: Dataset

2003–2004 National Health and Nutrition Examination Surveys (NHANES) (all women, n = 5152)

Inclusion Criteria:

- Completed both questionnaire and physical examination (n = 4912)
- Reproductive age (15 to 44 years) (n =1757)
- Not pregnant (n = 1482)
- Self-identified as Non-Hispanic White or Black, or Mexican American (n = 1372)
- Measurements for all biomarkers **(n = 1176, final sample)**
  - Neurotoxicants
    - Blood Pb (µg/dL) and blood MeHg (µg/L)
  - 10 biomarkers for allostatic load

Methods: Allostatic Load

AL is an indicator of chronic stress exposure

- AL biomarkers were dichotomized as high or low based on quartile cut-points (Chyu et al., 2011)
- **AL score=**Sum of high-risk biomarkers
  - **AL scores ≥4 ≈ chronic stress exposure** (Juster et al., 2010)
  - **AL scores 1-3 ≈ intermediate AL**
  - **AL score = 0 ≈ no chronic stress exposure**

Allostatic Load Biomarkers by System

Biomarker	Cut-point
Cardiovascular	
Heart Rate (beats/min)	>83
Mean Systolic BP (mm Hg)	>117
Mean Diastolic BP (mm Hg)	>75
Homocysteine (umol/L)	>7.9
Metabolic	
Body Mass Index (kg/m^2)	>31
HDL-Cholesterol (mg/dL)	<45
Total Cholesterol (mg/dL)	>209
Glycohemoglobin (%)	>5.3
Immune	
C-reactive protein (mg/dL)	>0.43
Albumin (g/dL)	<4.0

The Hazard Index (HI) is used here as an indicator of NDT

1. Calculate Hazard quotients (HQs)

- Individual blood concentration (E) divided by metal-specific health reference value (HRV)
  - **HRV_{Pb} = 1.75 µg/dL** (Jedrychowski et al., 2009)
  - **HRV_{MeHg} = 5.8 µg/L** (USEPA, 2001)

$$HQ = E/HRV$$

*2. Calculate the HI: Sum HQs**

$$HI = HQ_{Pb} + HQ_{MeHg}$$

- **HI >1 ≈ higher NDT hazard**
- **HI ≤1 ≈ lower NDT hazard**

*Dose-addition is assumed for the HI calculation because Pb and MeHg have similar NDT endpoints

Methods: Sociodemographic and Lifestyle Variables

Race/Ethnicity
- Non-Hispanic White (White)
- Non-Hispanic Black (Black)
- Mexican American

Age (years)
- 15-19, 20-26, 27-36, 37-44

Income ($1,000)
- <15, 15-55, >55

Poverty-to-income Ratio
- <2 *or* ≥2

Head of Household highest educational attainment
- Less than high school graduate
- High School/GED or some college/AA degree
- College graduate or more

Smoking status (blood cotinine)
- Non-smoker (<10 ng/mL)
- Smoker (≥10 ng/mL)

Physical Activity
- No *or* Yes

Methods: Data Analysis

The association between race/ethnicity and higher NDT hazard (HI >1) was examined using logistic regression

- Sampling weights were used to account for complex survey design and to produce unbiased, national estimates

- Covariates that changed the odds ratio (OR) between race/ethnicity and higher NDT hazard by ≥10% were included in the final model

- The final model was stratified by AL groups (0, 1–3, ≥4)

RESULTS

Population Characteristics

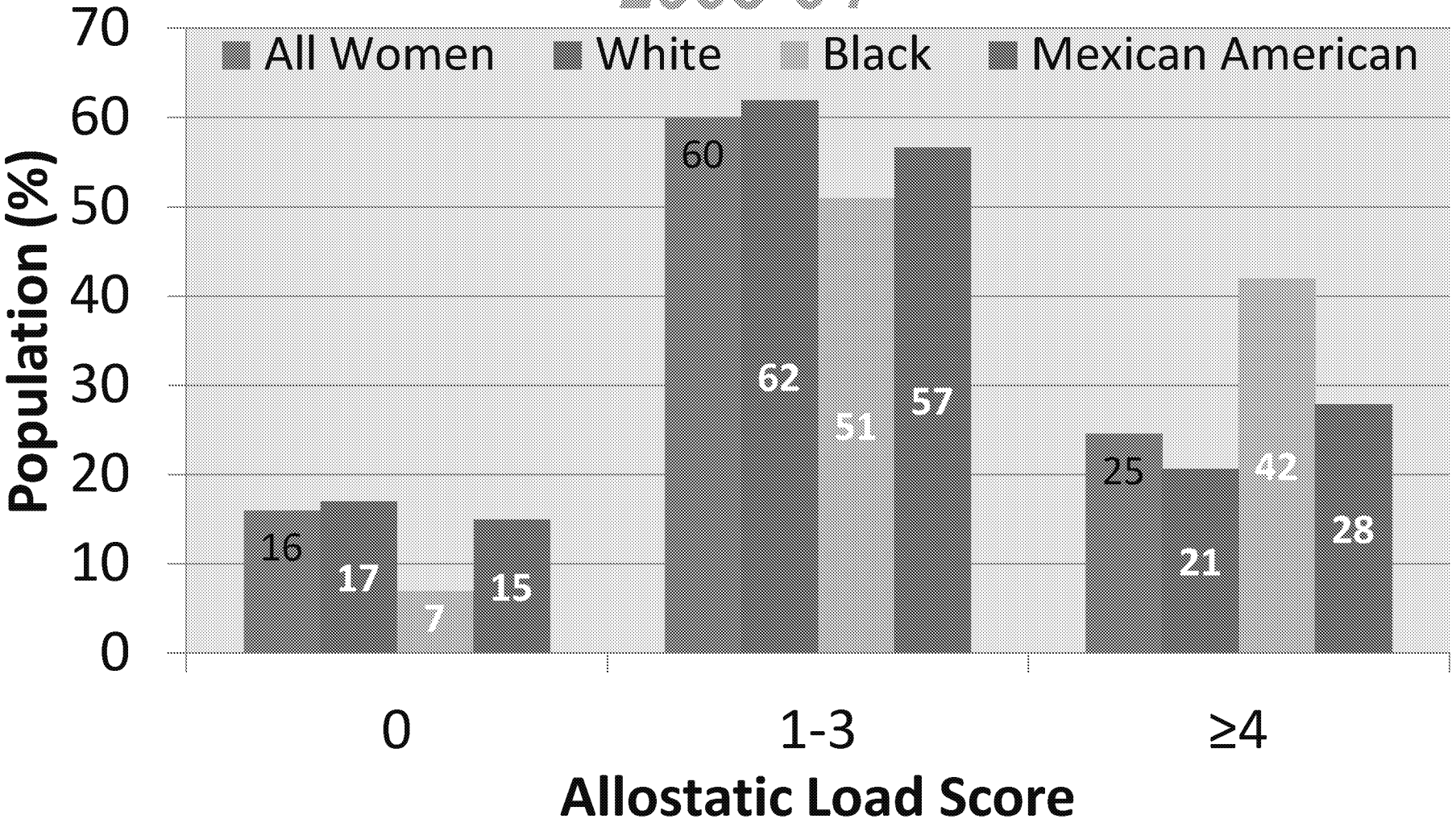
More likely to have chronic stress (AL≥4)

- Blacks
- Women 20-44 years (compared with 15-19 years)
- Lower SES
- Smokers
- No physical activity

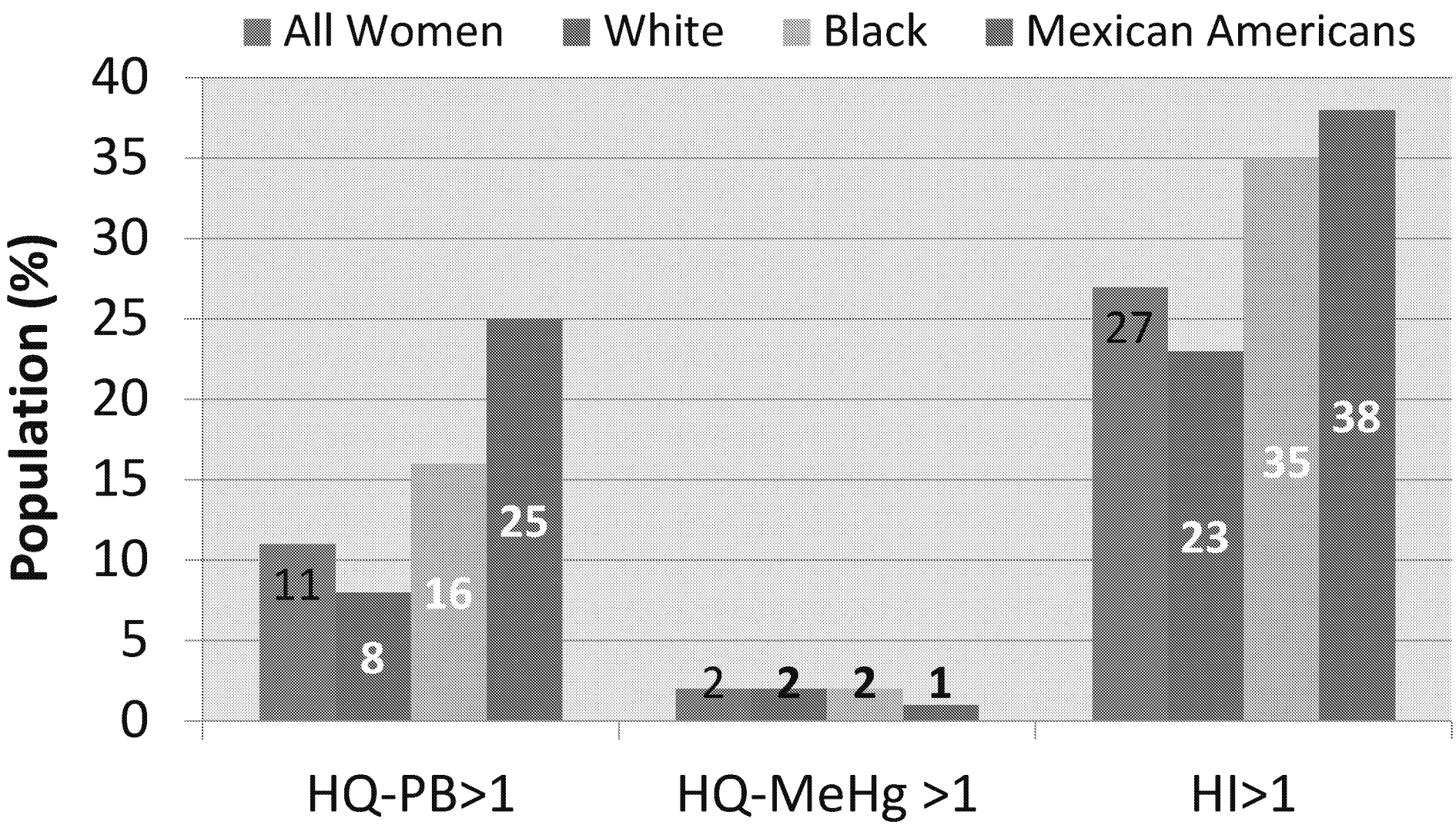
More concern with NDT hazard (HI>1)

- Blacks, Mexican Americans
- Women 20-44 years (compared with 15-19 years)
- Lower SES
- Smokers

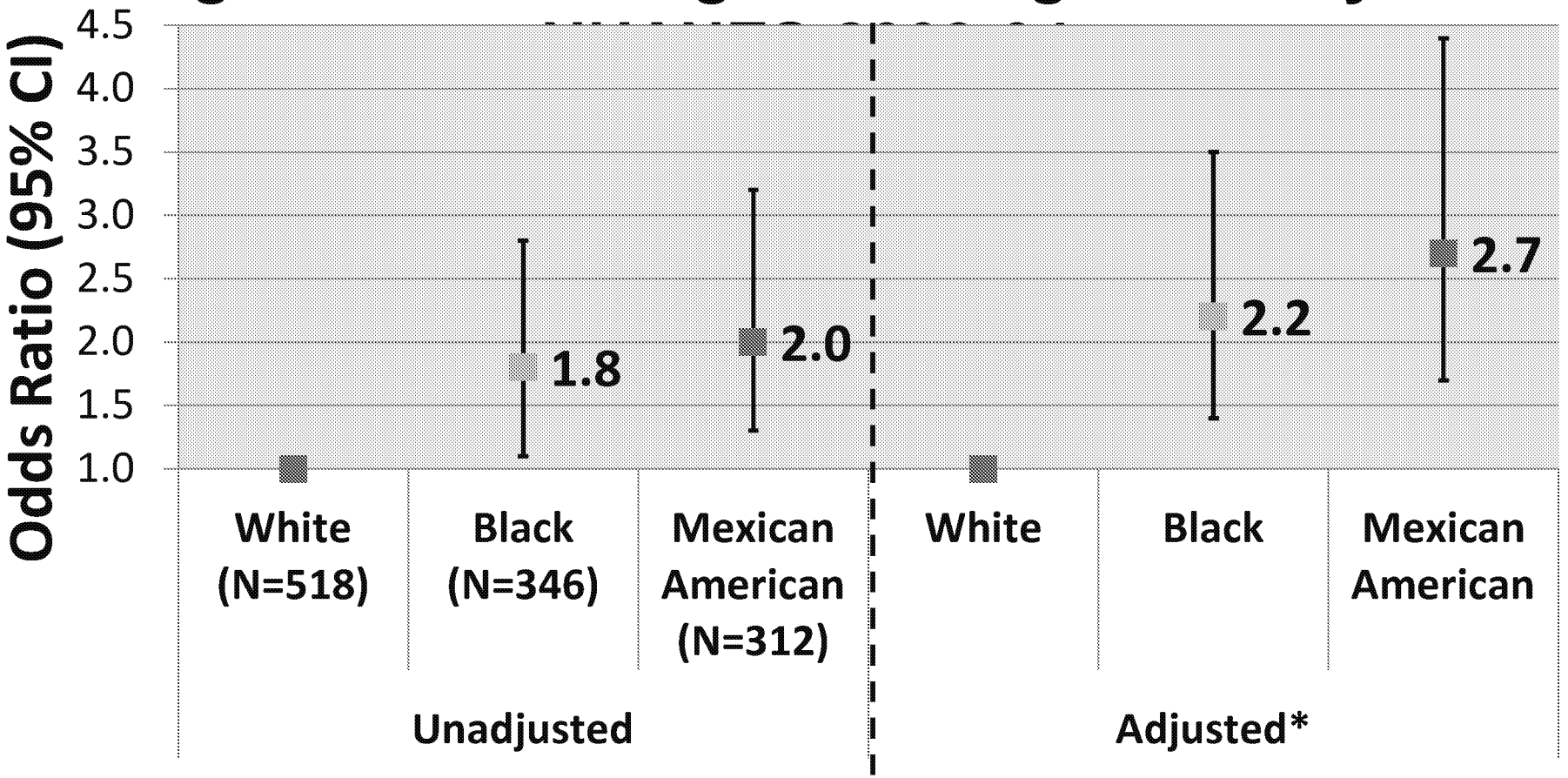
Percentage of women ages 15-44 years by AL group stratified by race/ethnicity in NHANES 2003-04



Percentage of population by NDT Hazard



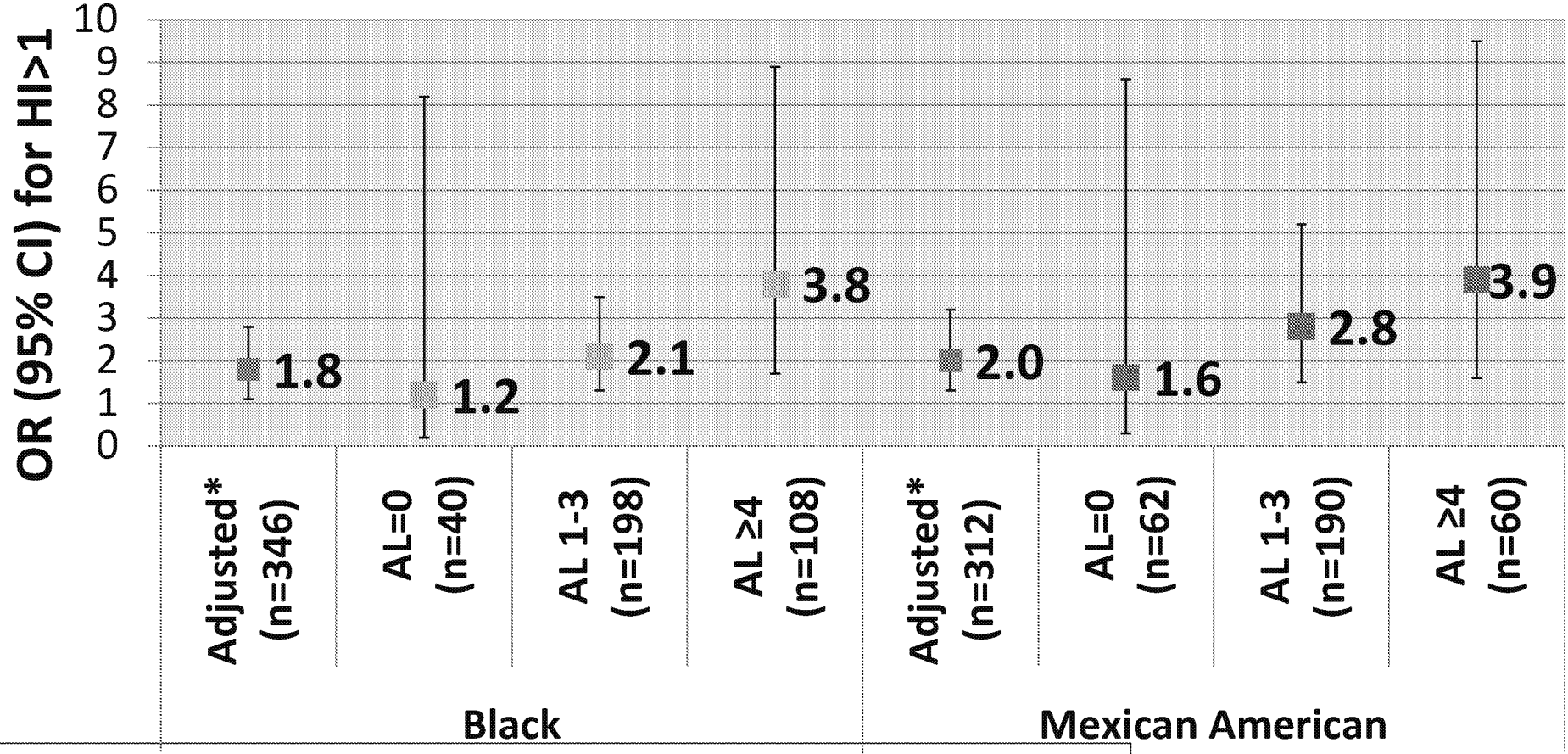
Association between race/ethnicity and odds of having an HI >1 among women ages 15-44 years in



Older (20-44 years), Non-White women who **smoke** were more likely to have an HI >1

*Adjusted for age, head of household education, and smoking

Results: Adjusted association between race/ethnicity and odds of having an HI >1 among women ages 15-44 years in NHANES 2003-04 stratified by AL score groups



Effect measure modification of race/ethnicity and HI>1 association by AL

*Adjusted for age, head of household education, and smoking

Discussion

- **Pb** was the main contributor to the HI
  - Mean HQ_{Pb} **3X higher** than the mean HQ_{MeHg} (0.6 vs. 0.2)
- Independent of age, education, and smoking, **Non-Whites were more likely than Whites to have an HI >1**
- AL modified the association between NDT hazard and race/ethnicity

Discussion: Limitations

- Use of exposures in non-pregnant women of reproductive age as surrogates of potential maternal/fetal exposures may not be representative of exposures during pregnancy
- Other stressors that may be associated with neurodevelopmental outcomes were not included
- Cross sectional data—One-time measurements performed on all stressors (AL biomarkers, Pb, MeHg)
- Used HI to examine higher joint Pb and MeHg exposures
  - May not reflect underlying mode of action
  - Uncertainty in using dose-addition for similar endpoint

Conclusions

- Chronic stress, a non-chemical stressor, was found to modify the association between race/ethnicity and likelihood NDT hazard
- This research highlights the importance of evaluating co-exposures (chemical and non-chemical) with a common endpoint
- Results from these analyses could identify potentially susceptible populations for future epidemiological studies or be used by risk managers